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(54) BENZAZEPINE DERIVATIVES

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Title: Benzoazepine Derivatives

Abstract:

5-HT_{2c} receptor agonist having a benzoazepine derivative or pharmaceutically acceptable salt thereof as effective component and novel benzoazepine derivatives that are 5-HT_{2c} receptor agonists, or pharmaceutically acceptable salts thereof.

SPECIFICATION
BENZOAZEPINE DERIVATIVES

TECHNICAL FIELD

The present invention relates to 5-HT_{2c} receptor agonist having a benzoazepine derivative or a pharmaceutically acceptable salt thereof as effective component.

Furthermore, the present invention relates to novel benzoazepine derivatives or pharmaceutically acceptable salts thereof.

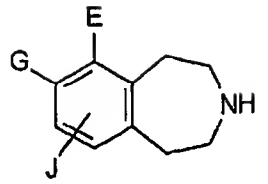
TECHNICAL BACKGROUND

The serotonin 2c (5-HT_{2c}) receptor is distributed mainly in the central nervous system, and although its role has not been enough clarified, it is believed to be involved in central nervous system disease such as sexual dysfunction, obesity, hyperphagia, anxiety depression and sleep disorder (*Curr. Opin. Invest. Drugs* 2 (4) 317 (1993)). Therefore, a 5-HT_{2c} receptor agonist is useful in the prophylaxis or the treatment of the above-mentioned diseases.

Tricyclic pyrroles or pyrazole derivatives (EP 657426, EP 700905, WO 98/56768 and the like), tetrahydropyrazinoquinoxaline derivatives (WO 00/35922) or tetracyclic gamma carboline derivatives (WO 00/77001 and the like) and the like have been reported as 5-HT_{2c} receptor agonists.

Meanwhile, numerous compounds have been reported as benzoazepine derivatives (NL 6802257, BE 719631, DE 2207430, EP 7070, EP 285287, WO 93/00094, WO 96/22290 and the like). Reported as benzoazepine derivatives having 2 to 3 substituents on the benzene ring in these reports are: compounds wherein, in the following formula (A), E or G represents -$S(O)_{0-2}$-(lower alkyl, trifluoromethyl, amino, mono or dimethylamino or phenyl) or acetyl; compounds wherein G represents amino and E and J represent chloro or bromo, compounds wherein G represents a hydroxyl group or methoxy and E or/and J are identical or different and represent a hydroxyl group, methoxy, bromo or nitro; and compounds wherein E and G represent chloro.

In addition, in terms of compounds having a heteroaromatic ring condensed on the benzene ring, a compound wherein the substituent on the heteroaromatic ring thereof always has a cyclic amine has been reported.



(A)

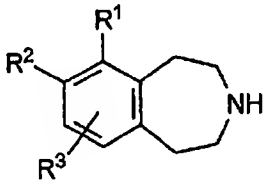
In addition, the reports on the above-mentioned benzoazepine derivatives describe a morphine receptor antagonist, a 5-HT_1 receptor agonist, a 5-HT_{2A} receptor agonist or a dopamine receptor antagonist; they also describe treatment of pain, anorexia, hypertension, ventriculus dyskinesia and schizophrenic disorder, as medical applications thereof.

However, in these reports, no description is made regarding 5-HT_{2c} receptor agonist activity or sexual dysfunction improvement activity, and benzoazepine derivatives having 5-HT_{2c} receptor agonist activity or sexual dysfunction improvement activity are not yet known.

DISCLOSURE OF THE INVENTION

The present inventors have earnestly investigated 5-HT_{2c} receptor agonists. As a result, they discovered that the benzoazepine derivative represented by the following Formula (I) had an excellent agonist activity on the 5-HT_{2c} receptor, and that among the compounds represented by Formula (I), the benzoazepine derivative represented by the following formula (II) having not less than 2 substituents on the benzene ring was a novel compound, and had an excellent agonist activity on the 5-HT_{2c} receptor; and [in this manner] the present invention was completed.

That is to say, the present invention relates to a 5-HL_{2c} receptor agonist having as an active component the zenzazepine [*sic*] derivative represented by the following Formula (I) or a pharmaceutically acceptable salt thereof.



(I)

(In the Formula, the symbols have the following meanings:

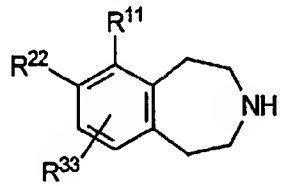
R^1, R^2 and R^3 may be identical or different and represent -H, lower alkyl that may be substituted, lower alkenyl that may be substituted, acyl, -OH, -O-hydrocarbon group that may be substituted, -SH, -S-hydrocarbon group that may be substituted, amino,

mono or di-lower alkyl amino acylamino, a nitrogen of which may be substituted with a lower alkyl, halo, nitro or cyano; furthermore, R^2 may, together with R^1 or the adjacent R^3, form a heteroaromatic ring that may be substituted.)

The 5-HT_{2c} receptor agonist (I) of the present invention is preferably a 5-HT_{2c} receptor agonist (I) of the present invention wherein R^1 and R^3 are identical or different and are -H, lower alkyl or halo, and R^2 represents lower alkyl or halo; more preferably, this is a 5-HT_{2c} receptor agonist (I) of the present invention wherein R^1 represents halo, R^2 represents lower alkyl or halo and R^3 represents –H; and particularly preferably, this is a 5-HT_{2c} receptor agonist (I) of the present invention, which is 6,7-dichloro-2,3,4,5-tetrahydro-1H-3-benzoazepine, 7-bromo-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine, 6-chloro-7-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine or pharmaceutically acceptable salts thereof.

The 5-HT_{2c} receptor agonist (I) of the present invention can be used as a therapeutic agent for a variety of central nervous system diseases. Preferably, the 5-HT_{2c} receptor agonist (I) of the present invention is a therapeutic agent for sexual dysfunction, and particularly preferably, it is a therapeutic agent for erectile insufficiency.

Furthermore the present invention relates to the benzoazepine derivative represented by the following Formula (II), or a pharmaceutically acceptable salt thereof.



(II)

(In the Formula, the symbols have the following meanings:

R^{11} and R^{33}: one of the two represents -H, lower alkyl, amino, mono- or di-lower alkylamino, acylamino that may have a lower alkyl on the nitrogen, halo, nitro or cyano; the other represents lower alkyl, amino, mono or di-lower alkylamino, acylamino that may have a lower alkyl on the nitrogen, halo, nitro or cyano;

R^{22} represents a lower alkyl, -OH, -O-lower alkyl, amino, mono- or di-lower alkylamino, acylamino, a nitrogen of which may be substituted by a lower alkyl, halo, nitro or cyano;

furthermore, R^{22} may, together with R^{11} or the adjacent R^{33}, form a heteroaromatic ring that may be substituted with lower alkyl, -OH or -O-lower alkyl;

however,

1) if R^{11} represents halo and R^{22} represents amino, R^{33} represents a group other than halo;

2) if R^{22} represents -OH or methoxy, R^{11} and R^{33} are identical or different and represent a group other than -OH, methoxy, bromo or nitro

3) if R^{11} represents chloro, R^{22} represents a group other than chloro)

The compound (II) of the present invention is preferably a compound (II) of the present invention wherein one among R^{11} and R^{33} represents -H, lower alkyl or halo, the other represents lower alkyl or halo, and R^{22} represents lower alkyl or halo; more preferably, this is a compound (II) of the present invention wherein R^{11} represents halo, R^{22} represents lower alkyl or halo, and R^{33} represents –H; and particularly preferably, this is a compound (II) of the present invention, which is 7-bromo-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine, 6-chloro-7-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine. or pharmaceutically acceptable salts thereof.

In the following, the compounds (I and II) of the present invention will be described in detail.

In the definition of the formulas in the present specification, unless otherwise stated, the term "lower" means a straight or branched carbon chain having 1 to 6 carbons.

Examples of "lower alkyls" include, for instance, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl or isohexyl; preferably methyl, ethyl, propyl or isopropyl; more preferably methyl or ethyl; and particularly preferably methyl.

Examples of "lower alkenyls" include, for instance, vinyl, 1-propenyl, allyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-butene-2-yl, 2-methyl-1-propenyl, 3-butene-2-yl, 2-methyl-2-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl or 5-hexenyl, preferably vinyl or allyl.

"Cycloalkyl" means a saturated mono- to tricyclic aliphatic hydrocarbon ring group having 3 to 14 carbons, and examples include, for instance, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclooctyl, bicyclononyl, bicyclodecanyl, tricycloundecanyl, tricyclododecanyl or tricyclotridecanyl; preferably cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

"Cycloalkenyl" means an unsaturated aliphatic hydrocarbon ring group, obtained by replacing 1 to 3 of any of the single bonds in the above-mentioned cycloalkyl group by double bonds, and examples include, for instance, cyclobutenyl, cyclopentenyl,

cyclohexenyl, cycloheptenyl or cyclooctenyl; preferably cyclopentenyl or cyclohexenyl.

"Aryl" means a mono- to tricyclic aromatic hydrocarbon ring group having 6 to 14 carbons, and examples include, for instance, phenyl, biphenyl, naphthyl, anthryl or phenanthryl; preferably phenyl or naphthyl.

"Heteroaromatic ring" means a 5 to 6 membered heteroaromatic ring having respectively 1 to 2 heteroatoms chosen from the group consisting of nitrogen, oxygen and sulphur, examples include pyrrole, imidazole, furan, oxazole, isoxazole, thiophene, thiazole, isothiazole, pyridine, pyridazine or pyrimidine; preferably, furan, thiophene, imidazole or oxazole; and particularly preferably, furan or thiophene.

Examples of "halo" include fluoro, chloro, bromo or iodo; preferably, fluoro, chloro or bromo; and particularly preferably chloro or bromo.

"Mono or di-lower alkylamino" means an amino substituted with 1 to 2 of the above-mentioned lower alkyls; preferably, methylamino or ethylamino; and particularly preferably methylamino.

"Acyl" means carbonyl, sulfinyl or sulfonyl substituted with –H or the above-mentioned lower alkyl, cycloalkyl, aryl, amino or mono or di-lower alkyl amino; preferably acetyl, propionyl, methane sulfonyl, ethane sulfonyl or benzene sulfonyl; and particularly preferably acetyl or methane sulfonyl.

"Acyl amino" means amino substituted with the above-mentioned acyl; preferably, acetylamino, propionylamino, methanesulfonylamino, ethanesulfonylamino or benzenesulfonylamino; and particularly preferably, acetylamino or methanesulfonylamino.

"Hydrocarbon group" means the above-mentioned lower alkyl, lower alkenyl, cycloalkyl, cycloalkenyl or aryl or a group resulting from substitution or condensation therebetween; preferably lower alkyl, cycloalkyl or aryl; and particularly preferably lower alkyl.

"May be substituted" means that this may be substituted with 1 to 4 substituents from 1 to 3 species, examples of these substituents including, for instance, lower alkyl, -OH, -O-lower alkyl, -SH, -S-lower alkyl, amino, mono or di-lower alkyl amino, acyl, -O-acyl, acyl amino, -COOH, -COO-lower alkyl, halo, nitro or cyano; preferably lower alkyl.

Depending on the nature of the substituent, optical isomers (optically active substances, diastereomers and the like) or geometric isomers of compounds (I and II) of the present invention exist. Consequently, the compounds (I and II) of the present invention include mixtures or isolates of these optical isomers or geometric isomers.

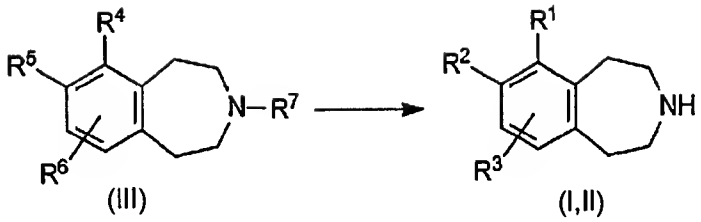
In addition, the compounds (I and II) of the present invention can form an acid addition salt or a salt with a base. Examples include, for instance, acid addition salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid or phosphoric acid, or organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, citric acid, tartaric acid, carbonic acid, picric acid, methanesulfonic acid, ethane sulfonic acid or glutamic acid, and salts with inorganic bases such as sodium, potassium, magnesium, calcium or aluminium, or organic bases such as methylamine, ethylamine, monoethanolamine, diethanolamine, triethanolamine, cyclohexyl amine, lysine or ornithine. In addition, the compounds (I and II) of the present invention or pharmaceutically acceptable salt thereof can form hydrates, solvates with ethanol and the like or polymorphic crystals.

In addition, the compounds (I and II) of the present invention also include all compounds that are metabolized and converted *in vivo* into the compounds (I and II) of the present invention or pharmaceutically acceptable salt thereof, which is to say, prodrugs. Examples of groups that form prodrugs for the compounds (I and II) of the present invention include the groups that are described in *Prog. Med.* 5:2157-2161 (1985), and the groups that are described in "Drug Development" Volume 7, Molecular Design, Hirokawa-Shoten, 163-198 (1990). Specifically, they are groups that can be converted by hydrolysis or solvolysis, or under physiological conditions, into the primary amines or secondary amines, -OH, -COOH [compounds] or the like of the present invention; for example, –OH prodrugs include -OC(O)-lower alkyl that may be substituted, -OC(O)-aryl that may be substituted, -OC(O)-lower alkylene that may be substituted-C(O)OR (R represents -H or lower alkyl; same hereinafter), -OC(O)-lower alkenylene that may be substituted-C(O)OR, -OC(O)–lower alkylene-O-lower alkylene-C(O)OR, -OC(O)-C(O)OR, -OC(O)-lower alkenylene that may be substituted-S(O)2OR, -O-phthalidyl, 5-methyl-1,3-dioxolene-2-one-4-yl-methyl oxy and the like.

Preparation Method

The compounds (I and II) of the present invention can be prepared by applying a variety of synthesis methods, by exploiting characteristics based on the fundamental backbone thereof or the type of substituent. In the following, representative preparation methods will be described.

Preparation 1

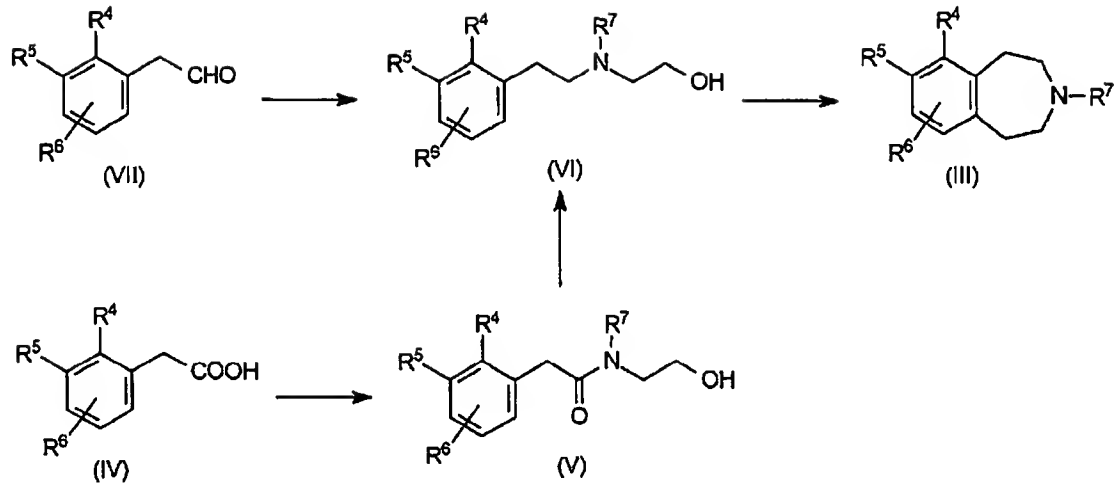


(In the formula, R^1, R^2 and R^3 have the meanings as described above. R^4, R^5 and R^6 respectively mean R^1, R^2 and R^3 or substituents that can be converted into R^1, R^2 and R^3 by a conventional chemical reaction. R^7 means -H or a nitrogen protecting group; Same hereinafter.)

The compounds (I and II) of the present invention can be prepared by converting the functional groups R^4, R^5 and R^6 of compound (III) so as to convert them to R^1, R^2 and R^3, respectively. For instance, in the case of a nitro group, this can be easily converted into chloro, bromo or cyano group or the like by reduction and reversion to amino, followed by the use of a Sandmaeyer reaction (*Org. Syn.* III. 185). In addition, in the case of an amino group, the substituent can be easily converted by acylation, alkylation or the like. If R^7 is a protecting group, the desired compounds (I and II) of the present invention can be prepared by deprotection (*Protective groups in Organic Synthesis*, Second Ed., JOHN WILEY & SONS, INC.). When R^1 and R^2 together form a furan ring, the compounds (I and II) of the present invention can be prepared from a compound wherein R^4 represents methoxy, according to the synthesis method described in *Synth. Comm.*, 257 (1989) or the like.

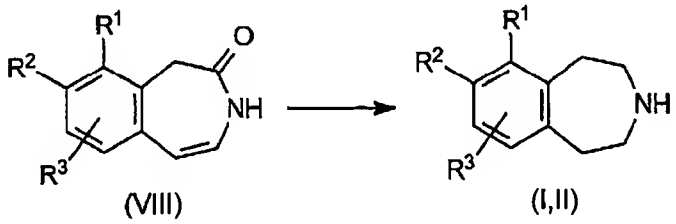
Synthesis of the Starting Material

The source compound (III) in Preparation 1 can be prepared according to the following method.



The source compound (III) for the compounds (I and II) of the present invention can be prepared according to the synthesis method described in *J. Med. Chem.*, 26, 1213 (1983). The compound (III) can be prepared, by deriving an amide compound (V) from a phenylacetic acid derivative (IV) according to a method of the art, further reducing to form a substituted amino ethanol compound (VI), converting the resulting hydroxyl group into a leaving group such as chloro group, and carrying out an intramolecular Friedel-Craft reaction in the presence of a suitable Lewis acid, such as aluminum chloride. In addition, the compound (VI) can also be prepared by a reductive amination reaction of the corresponding aldehyde compound (VII). The aldehyde compound (VII) can, for example, be prepared by the method described in US 493347, or the like.

Preparation 2



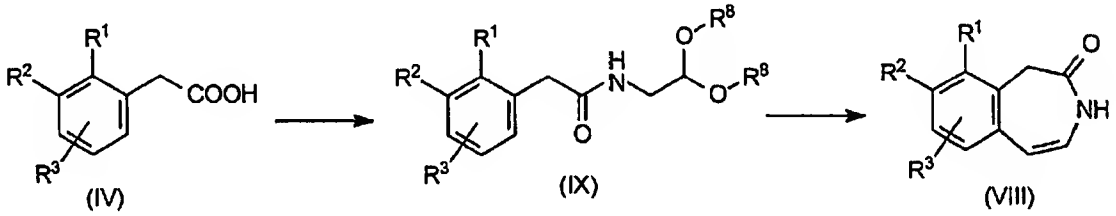
The compounds (I and II) of the present invention can be prepared by reducing compound (VIII).

Preparation is possible by reduction of the olefin portion of compound (VIII) by contact hydrogenation using, for instance, a metal catalyst such as palladium carbon, with acetic acid or ethanol, a mixed solvent thereof or the like as solvent, at ice-cold to room temperature, and reducing the amide portion using, for instance, a reducing agent

such as borane or aluminium lithium hydride, with tetrahydrofuran, dioxane or the like as solvent, at ice-cold to room temperature.

Synthesis of the Starting Material

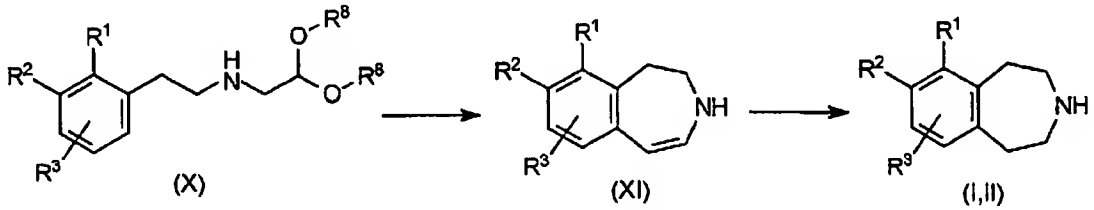
The source compound (VIII) of Preparation 2 can be prepared according to the following method.



(In the formula, R^8 represents a lower alkyl. Same hereinafter.)

The compound (VIII) can be prepared by adapting the synthesis method described in Japanese unexamined patent application JP-63-255226-A for the phenylacetic acid derivative (IV). The compound (VIII) can be prepared by deriving an amide compound (IX) from the phenylacetic acid derivative (IV) by a method of the art, and reacting under suitable acidic conditions with, for example, sulfuric acid, trifluoromethanesulfonic acid or the like as solvent.

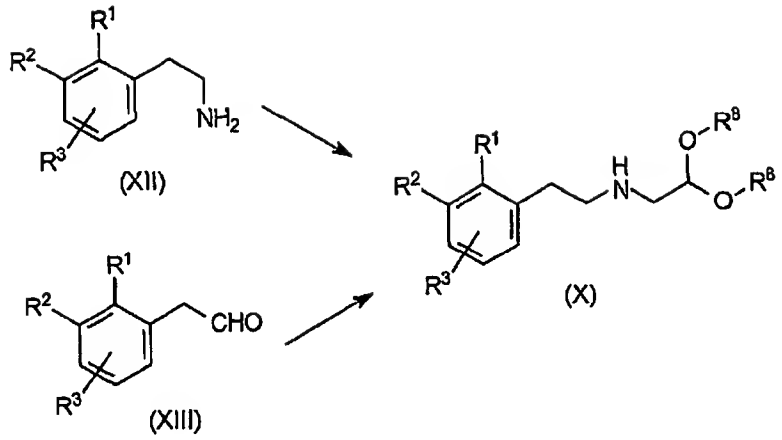
Preparation 3



The compounds (I and II) of the present invention can be prepared by reacting a compound (X) under suitable acidic conditions with, for example, sulfuric acid or trifluoromethanesulfonic acid as solvent, at ice-cold to room temperature, and reducing the olefin portion of the compound (XI) that is obtained, in the same manner as in Preparation 2.

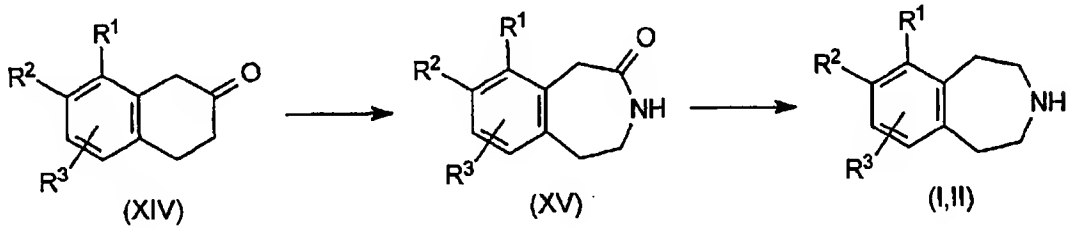
Synthesis of the Starting Material

The source compound (X) of Preparation 3 can be prepared according to the following method.



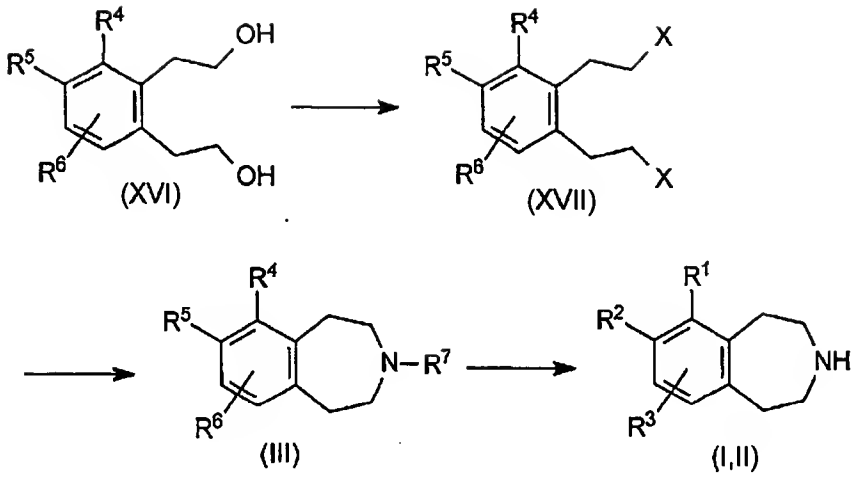
The aminoacetaldehyde dialkylacetal derivative (X) can be prepared by adapting the synthesis method described in Japanese unexamined patent application JP-55-108855-A for a phenethylamine derivative (XII). In addition, compound (X) can also be prepared by a reductive amination reaction with the corresponding aldehyde compound (XIII), or the like.

Preparation 4



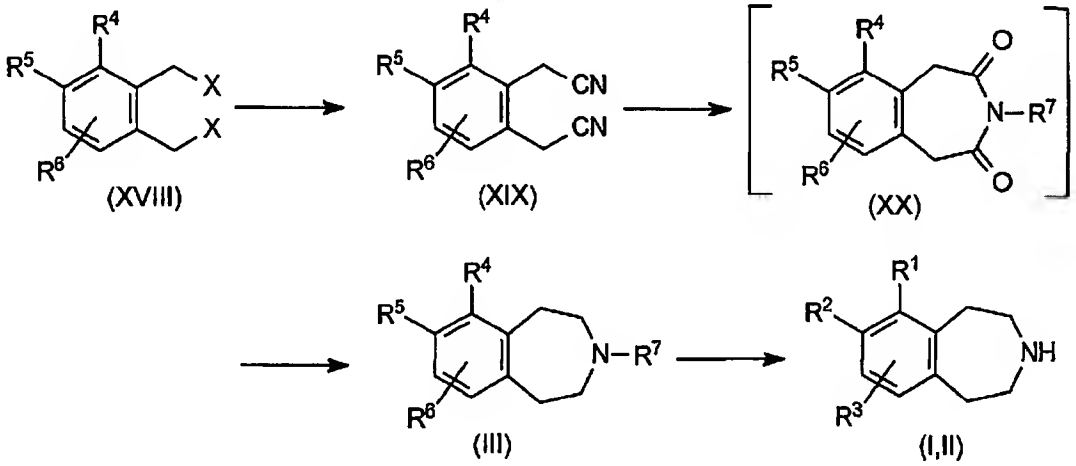
The compounds (I and II) of the present invention can be prepared by carrying out a Beckmann rearrangement reaction on a β-tetralone derivative (XIV) and reducing the obtained amide compound (XV) in the same manner as in Preparation 2. The Beckmann rearrangement reaction can be carried out with chloroform or methylene chloride or the like as a solvent, in the presence of a suitable acid, such as, in the presence of sulfuric acid, trifluoromethanesulfonic acid or the like, at ice-cold to room temperature. The starting material β-tetralone derivative (XIV) can be prepared by the synthesis method described in *Indian J. Chem.*, Sect. B: Org. Chem. Incl. Med. Chem., 37B (3), 281 (1998) or the like.

Preparation 5



(In the formula, X means tosyloxy, mesyloxy, halo or the like. Same hereinafter.) The compounds (I and II) of the present invention can be prepared according to the synthesis method described in *J. Org. Chem.*, 56, 2937 (1991) or the like. The compounds (I and II) of the present invention can be prepared by the action of a suitable amine on a compound (XVII), which can be prepared from 1,2-bis (hydroxyethyl)benzene derivative (XVI), to prepare compound (III), and subsequently following the method of Preparation 1.

Preparation 6



The compounds (I and II) of the present invention can be prepared according to the synthesis method described in *J. Med. Chem.*, 27, 918 (1984). They can be prepared from a compound (XVIII) having a desired substituent by deriving a cyano compound

(XIX) therefrom following a method of the art, subjecting this to an intramolecular cyclization reaction in the presence of a suitable acid and, passing through compound (XX), applying reducing conditions. In addition, the compounds (I and II) of the present invention can be prepared by directly applying intramolecular cyclization conditions to the cyano compound (XIX) in a reductive manner, so as prepare compound (III), and subsequently following Preparation Method 1.

The compounds (I and II) of the present invention prepared in this manner are isolated either in free form, or as salts thereof. A salt of a compound of the present invention can be prepared by subjecting the compound of the present invention in free base form to a conventional salt formation reaction.

Furthermore, the compounds (I and II) of the present invention or salts thereof are isolated and purified as hydrates thereof, solvates thereof, or polymorphic crystalline substances. The isolation and purification are carried out by applying conventional chemical procedures such as extraction, concentration, evaporation, crystallization, filtration, recrystallization, and various types of chromatography.

The various isomers can be separated by selecting a suitable source compound, or exploiting the differences in physical properties between the isomers. For instance, stereochemically pure isomers can be derived from optical isomers by selecting a suitable starting material, or by a method for resolving a racemic compound (for instance, a method for deriving diastereomeric salts of a common optically active acid, and optically resolving this, or the like).

Formulation

The compounds (I and II) of the present invention can be applied to a variety of formulations conventionally in use.

Representative formulations thereof are described in the following.

A medicinal composition having as effective component not less than 1 to 2 species of the compounds (I and II) of the present invention or pharmaceutically acceptable salts thereof can contain a pharmaceutically acceptable carrier; this is prepared as tablet, powder, subtle granule, granule, capsule, pill, solution, injectable, suppository/ointment, skin patch or the like, using a carrier, a diluting agent or other additives that are commonly used in drug preparation; and this is administered orally (including sublingual administration) or non-orally.

Clinical dosages of the compounds (I and II) of the present invention or pharmaceutically acceptable salts thereof in humans are suitably determined on a case-

by-case basis, with consideration for the symptoms, body weight, age and sex of the patient in which is to be used, the administration route and the like; in general, it is administered orally in a range of 1 mg to 1000 mg per day per adult, and preferably 10 mg to 200 mg, once daily or divided into several doses per day, or it administrated intravenously in a range of 1 mg to 500 mg per day per adult, once daily or divided into several doses per day, or it is continuously administered intravenously within a range of 1 hour to 24 hours. As a matter or course, as mentioned above, since the dose varies depending a variety of conditions, there are cases where smaller amounts than the above-mentioned doses are sufficient.

Tablets, powders, granules and the like are used as solid compositions for oral administration of the present invention. In such a solid composition, one or more active substance is mixed with at least one inactive diluent, for instance, lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone or magnesium metasilicate aluminate. The composition may, according to methods of the art, contain additives other than inactive diluents, for example, lubricants such as magnesium stearate, disintegrants such as starch and calcium cellulose glycolate, stabilizers such as lactose, and solubilizers such as glutamic acid or aspartic acid.

The tablet or pill may, if necessary, be coated with a sugar coating such as sucrose, gelatin, hydroxypropylcellulose and hydroxypropyl methylcellulose phthalate or with a gastrosoluble or enterosoluble film.

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs and the like, and contain commonly used inactive diluents, such as, purified water or ethanol. In addition to the inactive diluent, this composition may contain an adjuvant such as a solubilization or dissolution promoting agent, a wetting agent or a suspending agent, a sweetener, a flavorant, an aromatic agent or a preservative.

Injectables for non-oral administration include sterile-water based or non-water based solutions, suspensions and emulsions. Water based solutions and suspensions can contain, for instance, distilled water and physiological saline for injectables. For example, propylene glycol, polyethylene glycol, plant oils such as olive oil, alcohols such as ethanol, Polysorbate 80 (product name) and the like are available for non-water soluble solutions and suspensions. Such a composition may further contain additives such as an isotonization agent, a preservative, a wetting agent, an emulsifier, a dispersant, a stabilizer (for instance, lactose), and a solubilization or dissolution

promoting agent. These are sterilized by, for example, filtration through a bacteria-retaining filter, admixture of a bactericide or irradiation. These can also be prepared as sterile solid compositions and dissolved in sterile water or a sterile injection solvent prior to use.

For instance, the following example can be given for a tablet for oral administration; however, the present invention is not limited to this formulation example.

Formulation Example

3 mg tablet composition

Compound of the present invention	3 mg
D-mannitol	89.8 mg
Corn starch	22.4 mg
Hydroxypropyl cellulose	3.6 mg
Magnesium stearate	1.2 mg
Total	120 mg

3 mg Tablet Preparation Method

Using a fluid-bed granulating and coating apparatus, 15 mg of the compound of the present invention, 449 g of D-mannitol, and 112 g of corn starch are mixed homogeneously. This is steamed with 180 g of a solution of 10% hydroxypropyl cellulose and granulated. After drying, this is passed through a 20 mesh sieve and 6 g of magnesium stearate is added and mixed in; tablets are produced at 3 mg per tablet with a rotary tablet press using a 7 mm x 8.4R punch and die.

BEST MODE FOR CARRYING OUT THE INVENTION

In the following, the present invention will be described in more detail by way of examples; however, the present invention is not limited to these examples.

Preparation Examples

In the following, methods for preparing the compounds (I and II) of the present invention will be described in detail. Note that syntheses of the source compounds used in the examples are described as reference examples.

Reference Example 1

Using sodium triacetoxyborohydride, reductive amination of 2,3-dichlorobenzene acetaldehyde and 2-(methylamino)ethanol was carried out to obtain 2-[[2-(2,3-dichlorophenyl)ethyl]methylamino]ethanol.

Reference Example 2

After transforming the hydroxyl group of 2-[[2-(2,3-dichlorophenyl)ethyl]methylamino]ethanol into a chloro group using phosphorus pentachloride, an intramolecular Friedel-Craft reaction was carried out to obtain 6,7-dichloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine.

Reference Example 3

2,4-dichlorophenyl acetic acid was transformed into acid chloride using thionyl chloride, and reacted with 2-(methylamino)ethanol to obtain an amide compound. The amide compound obtained was reduced using 1 mol/L borane tetrahydrofuran to obtain 2-[[2-(2,4-dichlorophenyl)ethyl]methylamino]ethanol.

Reference Example 4

6,8-dichloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine was obtained by a method similar to that in Reference Example 2.

Reference Example 5

The nitrogen atom on 6-chloro-7-nitro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride obtained in Example 1 was protected using di-tert-butyl dicarbonate. This was reduced using iron powder to obtain 3-(tert-butoxycarbonyl)-7-amino-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine.

Reference Example 6

The compound obtained in Reference Example 5 was acetylated using acetyl chloride to obtain 7-acetylamino-3-(tert-butoxycarbonyl)-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine.

Reference Example 7

2,3-difluorophenylacetic acid and aminoacetaldehyde diethylacetal were amidated using 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride to obtain N-(diethoxyethyl)-2,3-difluorobenzene acetamide.

Reference Example 8

N-(diethoxyethyl)-2,3-difluorobenzene acetamide was cyclized using concentrated sulfuric acid and trifluoromethane sulfonic acid to obtain 1,3-dihydro-8,9-difluoro-2H-3-benzoazepine2-one.

Reference Example 9

6-methoxy-2,3,4,5-tetrahydro-1H-3-benzoazepine was demethylated using 48% hydrobromic acid to obtain 6-hydroxy-2,3,4,5-tetrahydro-1H-3-benzoazepine. With this, the nitrogen atom was acetylated using anhydrous acetic acid, then alkylated using

sodium hydride and bromoacetaldehyde diethylacetal to obtain 3-acetyl-6-(2,2-diethoxyethoxy)-2,3,4,5-tetrahydro-1H-3-benzoazepine.

Reference Example 10

Using di-tert-butyl dicarbonate, the nitrogen atom of 7,8,9,10-tetrahydro-6H-furo[2,3-g][3]benzoazepine was protected to obtain N-(tert-butoxycarbonyl)-7,8,9,10-tetrahydro-6H-furo[2,3-g][3]benzoazepine. This was ethylated using n-butyl lithium and ethyl iodide to obtain 2-ethyl-N-(tert-butoxycarbonyl)-7,8,9,10-tetrahydro-6H-furo[2,3-g][3]benzoazepine.

Reference Example 11

Using bromo acetaldehyde diethyl acetal, 2-(2-chloro-3-methoxyphenyl)ethyl amine was alkylated to obtain [2-(2-chloro-3-methoxyphenyl)ethyl]aminoacetaldehyde diethylacetal.

Reference Example 12

Using iron powder, 6-chloro-3-methyl-7-nitro-2,3,4,5-tetrahydro-1H-3-benzoazepine was reduced to obtain 7-amino-6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine.

Reference Example 13

Using a method similar to that in Reference Example 12, 7-amino-8-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine was obtained from 7-chloro-3-methyl-8-nitro-2,3,4,5-tetrahydro-1H-3-benzoazepine.

Reference Example 14

Using concentrated nitric acid, 7-amino-8-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine was nitrated in concentrated sulfuric acid to obtain 8-amino-7-chloro-3-methyl-6-nitro-2,3,4,5-tetrahydro-1H-3-benzoazepine. This was reacted with sodium nitrite in acetic acid and concentrated sulfuric acid, then deaminated by adding the resulting reaction solution to an aqueous solution of sodium hypophoshate and copper (II) oxide, to obtain 7-chloro-3-methyl-6-nitro-2,3,4,5-tetrahydro-1H-3-benzoazepine.

Reference Example 15

Using succinic anhydride and aluminum chloride, 4-bromo-1,2-dimethyl benzene was acylated to obtain a mixture of 3-(2-bromo-4,5-dimethyl benzoyl) propionic acid and 3-(5-bromo-2,3-dimethyl benzoyl) propionic acid. By reducing this mixture using hydrazine, a mixture of 4-(2-bromo-4,5-dimethylphenyl)butanic acid and 4-(5-bromo-2,3-dimethylphenyl)butanic acid was obtained. To this mixture in acetic anhydride, 85% phosphoric acid was added for cyclization to obtain 5-bromo-7,8-dimethyl-3,4-dihydro-

1(2H)-naphthalenone.

Reference Example 16

Using triacetoxy sodium borohydride, reductive amination of 4.61 ml of (3-chloro-2-methylphenyl) acetaldehyde and amino acetaldehyde diethylacetal was carried out to obtain 2-(3-chloro-2-methylphenyl)ethyl]aminoacetaldehyde diethylacetal.

Reference Example 17

With 1,3-dichloro-2-ethyl benzene in tetrahydrofuran, and using 1,2-dibromo ethane and magnesium, a solution of (3-chloro-2-ethylphenyl)magnesium-tetrahydrofuran chloride was prepared. This was reacted with 2-chloro-N-methoxy-N-methyl acetamide to obtain 2-chloro-1-(3-chloro-2-ethylphenyl)ethanone.

Reference Example 18

Using aluminium lithium hydride, 2-chloro-3-methylbenzene acetonitrile was reduced to obtain 2-chloro-3-methylbenzene ethanamine.

Reference Example 19

Using sodium hydride and ethyl diethylphosphonoacetate, ethyl 4,5,6,7-tetrahydro-4-oxobenzo[b]thiophene-5-acetic ester was reacted to obtain ethyl 5-ethoxycarbonylmethyl-6,7-dihydro-5H-benzo[b]thiophene-4-ylidene acetic ester. This was reacted using 10% palladium carbon to obtain 4,5-bis(ethoxycarbonylmethyl)benzo[b]thiophene, then reduced using aluminium lithium hydride to obtain 4,5-bis(2-hydroxyethyl)benzo[b]thiophene.

Reference Example 20

Using a 1.6 M solution of butyl lithium hexane and ethyl bromoacetate, 2-methoxy-6,7-dihydro-5H-benzo[b]thiophene-4-one was reacted to obtain ethyl 2-methoxy-4,5,6,7-tetrahydro-4-oxobenzo[b]thiophene-5-acetic ester.

Reference Example 21

Using sodium hydride and bromoacetaldehyde diethylacetal, 3,4-dimethylphenol was reacted to obtain 3,4-dimethyl-1-(2,2-diethoxyethoxy)benzene. This was cyclized using polyphosphoric acid to obtain a mixture of 4,5-dimethylbenzofuran and 5,6-dimethyl benzofuran. This mixture was brominated with N-bromosuccinic imide, then reacted with sodium cyanide to obtain a mixture of 4,5-bis cyanomethylbenzofuran and 5,6-bis cyanomethylbenzofuran. This mixture was cyclized in an acetic acid solution of hydrogen bromide, then reduced using 10 M borane-dimethyl sulfide complex to obtain a mixture of 6,7,8,9-tetrahydro-5H-furo[2,3-h][3]benzoazepine and 7,8,9,10-tetrahydro-6H-furo[312-g][3]benzoazepine. With this mixture, nitrogen atoms were protected using di-

tert-butyl dicarbonate to obtain 7-(tert-butoxycarbonyl)-6,7,8,9-tetrahydro-5H-furo[2,3-h][3]benzoazepine (21a) and 8-(tert-butoxycarbonyl)-7,8,9,10-tetrahydro-6H-furo[3,2-g][3]benzoazepine (21b).

Reference Example 22

Using sodium borohydride, the compound obtained in Reference Example 15 was reacted to obtain 5-bromo-7,8-dimethyl-1,2,3,4-tetrahydro-1-naphthol. Next, this was reacted using p-toluene sulfonate-hydrate to obtain 8-bromo-5,6-dimethyl-1,2-dihydronaphthalene. This was oxidized using m-chloroperoxybenzoic acid to obtain 5-bromo-7,8-dimethyl-1,2,3,4-tetrahydro-1,2-epoxynaphthalene. This was reacted using trifluoroboron-diethyl ether complex to obtain 5-bromo-7,8-dimethyl-3,4-dihydro-2(1H)-naphthalenone.

Example 1

To a mixed solution of 2.04 g of 6-chloro-3-methyl-7-nitro-2,3,4,5-tetrahydro-1H-3-benzoazepine and 17 ml of 1,2-dichloro ethane, 1 ml of 1-chloroethyl chloroformate was added, and the solution was stirred overnight under heated reflux. The solvent of the reaction solution was removed by evaporation *in vacuo*, 15 ml of methanol was added to the residue, which was stirred for 5 hours under heated reflux, and then the solvent was removed by evaporation *in vacuo*. Water and a saturated aqueous solution of sodium hydrogen carbonate, in the amounts of 50 ml each, were added to the residue, which was extracted with chloroform (50 ml x 2); and after the extract was dried with anhydrous sodium sulfate, the solvent was removed by evaporation *in vacuo*. The residue was purified by silica gel column chromatography to obtain 1.06 g of a colorless oily substance. The oily substance obtained above was dissolved in 20 ml of ethyl acetate, 1.5 ml of 4 mol/L hydrochloric acid-ethyl acetate was added, and the deposited insoluble matter was collected by filtration to obtain 1.2 g of 6-chloro-7-nitro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride as a white solid.

The compounds of Example 2 to 4 were obtained by a method similar to that in Example 1.

Example 2: 7-chloro-8-nitro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride

Example 3: 6,8-dichloro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride

Example 4: 6,7-dichloro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride

Example 5

A solution of 4 mol/L hydrochloric acid-ethyl acetate in the amount of 0.5 ml was added to a mixed solution of 90 mg of 3-(tert-butoxycarbonyl)-7-amino-6-chloro-2,3,4,5-

tetrahydro-1H-3-benzoazepine obtained in Reference Example 5, 2 ml of ethyl acetate and 1 ml of methanol, and this was stirred for 2 hours at room temperature. The solvent of the reaction solution was removed by evaporation *in vacuo* and the residue was washed with ethyl acetate to obtain 80 mg of 7-amino-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride as a white solid.

Example 6

7-acetyl amino-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained by a method similar to that in Example 5.

Example 7

Methane sulfonyl chloride in the amount of 0.05 ml was added to a mixed solution of 0.18 g of 3-(tert-butoxycarbonyl)-7-amino-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine, 0.09 ml of triethylamine and 2 ml of 1,2-dichloroethane on ice, and this was stirred overnight at room temperature. A saturated aqueous solution of sodium hydrogencarbonate in the amount of 30 ml was added to the reaction solution; this was extracted with chloroform (50 ml × 2); and after the extract was dried with anhydrous sodium sulfate, the solvent was removed by evaporation *in vacuo*. The residue was purified by silica gel column chromatography to obtain 85 mg of 3-(tert-butoxycarbonyl)-6-chloro-7-mesylamino-2,3,4,5-tetrahydro-1H-3-benzoazepine as colorless caramel, and 6-chloro-7-mesylamino-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained by a method similar to that in Example 5.

Example 8

On ice, 30 mg of sodium hydride (60%) and 0.05 ml of methyl iodide were added to a mixed solution of 0.23 g of 7-acetylamino-3-(tert-butoxycarbonyl)-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine and 3ml of N,N-dimethyl formamide, and this was stirred for 5 hours at room temperature. Ethyl acetate in the amount of 50 ml was added to the reaction solution, which was washed with water and saturated saline and dried with anhydrous sodium sulfate, whereafter the solvent was removed by evaporation *in vacuo*. The residue was purified by silica gel column chromatography to obtain 0.21 g of 3-(tert-butoxycarbonyl)-6-chloro-7-acetyl methylamino-2,3,4,5-tetrahydro-1H-3-benzoazepine as a colorless non-crystalline powder, and 7-acetyl methylamino-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained by a method similar to that in Example 4.

Example 9

After a mixed solution of 100 mg of 7-acetyl methylamino-6-chloro-2,3,4,5-

tetrahydro-1H-3-benzoazepine and 2 ml of concentrated hydrochloric acid was stirred for 2 hours at 100°C, the solvent of the reaction solution was removed by evaporation. After the residue was washed with acetonitrile, the crude crystal obtained was dispersed in 30 ml of an aqueous solution of saturated sodium bicarbonate and extracted with ethyl acetate (50 ml x 2); and after the extract was washed with water and saturated saline, and dried with anhydrous sodium sulfate, the solvent was removed by evaporation *in vacuo*. The residue was dissolved in 3 ml of methanol and 3 ml of ethyl acetate, 0.4 ml of 4 mol/L hydrochloric acid-ethyl acetate was added, and the solution was stirred for 1 hour at room temperature, whereafter the solvent was removed by evaporation *in vacuo*. The residue was washed with ethyl acetate to obtain 45 mg of 6-chloro-7-methylamino-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride as a white solid.

Example 10

1,3-dihydro-8,9-difluoro-2H-3-benzoazepine-2-one in the amount of 0.26 g was dissolved in 5 ml of acetic acid, to which 50 mg of 10% palladium carbon was added, and the solution was stirred for 5 hours under hydrogen flow. After completion of the reaction, undissolved substances were removed by Celite filtration, and the filtrate was concentrated. A solution of 1 M borane tetrahydrofuran (3.3 ml) was added to this reductant, which was stirred overnight at room temperature. After 2 ml of methanol was added to the reaction solution, 5 ml of 1 mol/L aqueous hydrochloric acid was added and the solution was refluxed for 2 hours. After cooling the reaction solution, the solvent was removed by evaporation *in vacuo*, 15 ml of water and 5 ml of 1 mol/L sodium hydroxide were added to the obtained residue, and then the solution was extracted with chloroform. The organic layers were combined and dried with anhydrous sodium sulfate, whereafter the solvent was removed by evaporation *in vacuo*, and the residue was purified using silica gel column chromatography. The purification product obtained was dissolved in 0.5ml of a solution of 4mol/L hydrochloric acid-ethyl acetate and stirred. The precipitate was collected by filtration and dried *in vacuo* to obtain 0.14 g of 6,7-difluoro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride as a white solid.

Example 11

7-fluoro-6-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained by a method similar to that in Example 10.

Example 12

On ice, 150 g of 2-(2-chloro-3-methoxyphenyl)ethyl]aminoacetaldehyde diethylacetal was added to 10 ml of concentrated sulfuric acid and stirred for 1 hour at

room temperature. The reaction solution was dumped into cold water and neutralized by adding an aqueous solution of 2 mol/L sodium hydroxide and extracted using ethyl acetate. The organic layers were combined, washed using water and saturated saline and then dried with anhydrous magnesium sulfate. After removal of solvent by evaporation, the residue was purified by silica gel column chromatography to obtain 85 mg of 9-chloro-8-methoxy-2,3-dihydro-1H-3-benzoazepine. This was dissolved in a mixed solvent of 2 ml tetrahydrofuran and 2 ml of 0.5 M sodium dihydrogenphosphate aqueous solution, and 0.25 g of sodium cyanoborohydride was added, and a reaction was carried out for 1 hour at room temperature. Saturated aqueous sodium bicarbonate was added to the reaction solution, chloroform was added, and the organic layer was separated. The aqueous layer was washed using chloroform, and the organic layers were combined and dried with anhydrous magnesium sulfate. After removal of solvent by evaporation, the residue was purified by silica gel column chromatography, the pale yellow oily substance that was obtained was dissolved in a solution of 4 mol/L hydrochloric acid-ethyl acetate, and the crystal that precipitated was collected by filtration and dried *in vacuo* to obtain 54 mg of 6-chloro-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride as a white solid.

Example 13

An aqueous solution of 47% hydrogen bromide in the amount of 1 ml was added to an aqueous solution (2.5 ml) of 0.40 g 7-amino-6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine, which was subjected to heated reflux for 20 minutes. The reaction solution was cooled on ice, 0.13 g of sodium nitrite was added in small amounts in such a way that the temperature of the reaction solution did not exceed 10°C, whereafter the solution was stirred for 20 minutes. This reaction solution was instilled to a solution wherein an aqueous solution (2 ml) of 0.33 g of copper (I) bromide and 0.65 ml of a 47% aqueous solution of hydrogen bromide had been mixed on ice, so that the temperature of the reaction solution did not exceed 10°C, then stirred for 2 hours. The reaction solution was dumped into ice water, alkalinized by adding an aqueous solution of 1 mol/L sodium hydroxide, then extracted using ethyl acetate and dried with anhydrous sodium sulfate. After removal of solvent by evaporation *in vacuo*, the residue was purified by silica gel column chromatography to obtain 0.16 g of 7-bromo-6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine as a light brown oily substance, and 47 mg of 7-bromo-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained as a colorless solid by a method similar to that in Example 1.

Example 14

An amount of 3.13 g of and aqueous solution (9 ml) of potassium cyanide was added to 1.19 g of an aqueous solution (5 ml) of copper (I) chloride, and the solution was stirred for 30 minutes at room temperature, whereafter 32 ml of benzene was added to prepare a solution of copper (I) cyanide. On ice, 0.59 g of sodium nitrite was added in small amounts to 1.20 g of 7-amino-6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine in an aqueous solution of 2N hydrochloric acid (2 ml) so that the temperature of the reaction solution did not exceed 10°C, and then the solution was stirred for 30 minutes. Toluene in the amount of 24 ml was added to this reaction solution, and the aqueous layer was neutralized with sodium carbonate. On ice, this solution was instilled into the solution of copper (I) cyanide that was prepared beforehand in such a way that the temperature of the reaction solution did not exceed 10°C, and then stirred for 30 minutes, returned to room temperature and stirred overnight. After the reaction solution was diluted with ethyl acetate, it was washed using an aqueous solution of 10% sodium carbonate and dried with anhydrous sodium sulfate. After removal of solvent by evaporation *in vacuo*, the residue was purified by silica gel column chromatography to obtain 0.75 g of 6-chloro-7-cyano-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine as a light brown solid, and 428 mg of 6-chloro-7-cyano-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained as a colorless solid by a method similar to that in Example 1.

Example 15

Using a method similar to that in Reference Example 8, 6-amino-7-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine was obtained, and 7-chloro-6-bromo-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained using a method similar to that in Example 13.

Example 16

7-amino-6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine in the amount of 0.58 g was dissolved in 1.26 ml of an aqueous solution of 48% tetrafluoroboric acid, 0.19 g of sodium nitrate was added in small amounts on ice, whereafter the solution was stirred for 1 hour. After the water of the reaction solution was removed by evaporation *in vacuo*, the solution was stirred for 3 hours at 160°C. After cooling the reaction solution, this was diluted with saturated ammonia water, then extracted using chloroform and dried with anhydrous sodium sulfate. After removal of solvent by evaporation *in vacuo*, the residue was purified by silica gel column chromatography to obtain 0.48 g of 6-

chloro-7-fluoro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine as a light brown oily substance, and 6-chloro-7-fluoro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained using a method similar to that in Example 1.

Example 17

5-bromo-7,8-dimethyl-3,4-dihydro-2(1H)-naphthalenone in the amount of 0.79 g was dissolved in 45 ml of chloroform, 19 ml of concentrated sulfuric acid was added on ice, the solution was stirred for 5 minutes at room temperature, 406 mg of sodium azide was added over 25 minutes, and then the solution was stirred for 7 hours at room temperature. After dumping the reaction solution on ice and dissolution, the organic layers, which had been extracted with chloroform and combined, were washed with saturated aqueous sodium bicarbonate and saturated saline, whereafter the solution was dried with anhydrous sodium sulfate, and the solvent was removed by evaporation to obtain 718 mg of a mixture of 6-bromo-8,9-dimethyl-2-oxo-2,3,4,5-tetrahydro-1H-3-benzoazepine and 6-bromo-8,9-dimethyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzoazepine. The step described above was repeated once, 816 mg of the mixture obtained was dissolved in 75 ml of tetrahydrofuran, whereafter 1N borane-tetrahydrofuran complex and 15.2 ml of tetrahydrofuran solution were added, and the soution was stirred for 1 hour at room temperature and 2 hours at 60°C. After adding 152 ml of 1 mol/L aqueous hydrochloric acid to the reaction solution and subjecting this to heated reflux for 40 minutes, the solution was alkalinized with an aqueous solution of 1 mol/L sodium hydroxide and extracted with chloroform; the combined organic layer was washed with saturated saline, then dried with anhydrous sodium sulfate; the solvent was removed by evaporation; the residue was purified by silica gel column chromatography; and the product obtained was treated with a solution of 4mol/L hydrochloric acid-ethyl acetate to obtain 161 mg of 9-bromo-6,7-dimethyl-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride as a colorless solid.

Example 18

9-bromo-6,7-dimethyl-2,3,4,5-tetrahydro-1H-3-benzoazepine in the amount of 128 mg was dissolved in 20 ml of ethanol, 20 mg of 10% palladium carbon was added, and the solution was stirred overnight at room temperature under hydrogen at 1 atmosphere. After Celite filtration of the reaction solution, the solvent was removed by evaporation and saturated aqueous sodium bicarbonate was added, whereafter the organic layers that had been extracted with ethyl acetate and combined were washed with saturated saline, and then dried with anhydrous potassium carbonate and the solvent was

removed by evaporation. The same reaction procedure was carried out again until disappearance of the starting materials was confirmed; and after Celite filtration of the reaction solution, the solvent was removed by evaporation, the product obtained was treated with a solution of 4 mol/L hydrochloric acid-ethyl acetate, and this was recrystallized from ethanol-diethyl ether to obtain 50 mg of 6,7-dimethyl-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride as a colorless solid.

Example 19

7-chloro-6-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained using a method similar to that in Example 12.

Example 20

7-chloro-6-ethyl-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained using a method similar to that in Reference Example 16 and Example 12.

Example 21

6-chloro-7-methyl-2,3,4,5-tetrahydro-rH-3-benzoazepine hydrochloride was obtained using a method similar to that in Reference Example 11 and Example 12.

Example 22

Polyphosphoric acid in the amount of 1.65 g was added to a benzene solution (30 ml) containing 1.65 g of 3-acetyl-6-(2,2-diethoxyethoxy)-2,3,4,5-tetrahydro-1H-3-benzoazepine obtained in Reference Example 9, which was subjected to heated reflux for 30 minutes. After cooling the reaction solution, the organic layer and polyphosphoric acid were separated, the organic layer was diluted with ethyl acetate, washed using water and saturated saline and dried with anhydrous magnesium sulfate. After removal of solvent by evaporation, the residue was purified by silica gel column chromatography, to obtain a 2:3 mixture of product and starting materials. The mixture obtained was dissolved in 20 ml of methanol, 9 ml of an aqueous solution of 40% potassium hydroxide was added and the reaction was performed for 4 hours at 70°C. After cooling the reaction solution, this was extracted using chloroform and the organic layers were combined, washed using water and saturated saline, and then dried with anhydrous magnesium sulfate. After removal of solvent by evaporation, the residue was dissolved in tetrahydrofuran, 0.50 g of di-tert-butyl dicarbonate was added, and the solution was stirred for 1 hour at room temperature. After removal of solvent by evaporation, the residue was purified by silica gel column chromatography and the product obtained was treated with a solution of 4 mol/L hydrochloric acid-ethyl acetate to obtain 28 mg of 7,8,9,10-tetrahydro-6H-furo[2,3-g][3]benzoazepine hydrochloride as a colorless solid.

The compounds of Examples 23 to 25 were obtained by a method similar to that in Example 5.

Example 23: 2-ethyl-7,8,9,10-tetrahydro-6H-furo[2,3-g][3]benzoazepine hydrochloride

Example 24: 6,7,8,9-tetrahydro-5H-furo[2,3-h][3]benzoazepine hydrochloride

Example 25: 7,8,9,10-tetrahydro-6H-furo[3,2-g][3]benzoazepine hydrochloride

Example 26

After 300 mg of 4,5-bis (2-hydroxyethyl) benzo[b]thiophene was dissolved in 10 ml of tetrahydrofuran and cooled to -20 degrees, 540 mg of chloro p-toluene sulfonic acid, 393 µl of triethylamine and a catalytic amount of dimethylaminopyridine were added, and the solution was stirred for 113 hours at room temperature. Thereafter, 540 mg of chloro p-toluene sulfonic acid and 393 µl of triethylamine were further added, and the solution was stirred for 24 hours at room temperature. After the reaction solution was filtered and washed with diethyl ether, the filtrate was sequentially washed with an aqueous solution of 10% citric acid, saturated aqueous sodium bicarbonate and saturated saline. After the organic layer was dried with magnesium sulfate, the solvent was removed by evaporation, the residue was purified by silica gel column chromatography and somewhat concentrated, whereafter 30 ml of dioxane was added, and concentration was carried out *in vacuo* until the amount of solvent was about 15 ml. Potassium carbonate in the amount of 3.00 g was added to this solution and a mixed solution of 516 µl of benzylamine and 10 ml of dioxane was instilled over 1 hour under heated reflux. After a further 40 hours of heated reflux, the reaction solution was cooled and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography to obtain 269 mg of 8-benzyl-7,8,9,10-tetrahydro-6H-thieno[3,2-g][3]benzoazepine, and 7,8,9,10-tetrahydro-6H-thieno[3,2-g][3]benzoazepine hydrochloride was obtained by a method similar to that in Example 1.

Example 27

2-methoxy-7,8,9,10-tetrahydro-6H-thieno[3,2-g][3]benzoazepine hydrochloride was obtained from 2-methoxy-4,5,6,7-tetrahydro-4-oxo benzo[b] thiophene-5-ethyl acetate ester using a method similar to that in Reference Example 15 and Example 26.

The structural chemical formulas and the physicochemical characteristics of the compounds obtained in the reference examples and the examples are shown in the following tables.

The symbols in the tables have the following meanings.

Rf.: Reference Example Number

Ex.: Example Number

Ac: acetyl

Me: methyl

Et: ethyl

Pr: propyl

iPr: isopropyl

Allyl: allyl

Ph: phenyl

NMR: nuclear magnetic resonance spectrum (internal reference: DMSO-d_6, TMS, unless otherwise noted) δ:

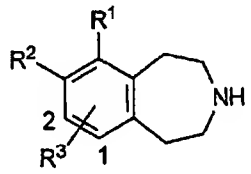
Table 1

Rf.	Data
1	NMR:2.26(3H, s), 2.42-2.50(2H, m), 2.53-2.62(2H, m), 2.84-2.93(2H, m), 3.40-3.48(2H, m), 3.64(1H, t), 7.28(1H, dd), 7.36(1H, dd), 7.48(1H, dd)
2	NMR:2.23(3H, s), 2.42-2.50(4H, m), 2.87-2.94(2H, m), 3.11-3.19(2H, m), 7.14(1H, d), 7.37(1H, d)
3	NMR($CDCl_3$):2.35(3H, s), 2.55-2.70(4H, m), 2.83-2.92(2H, m), 3.52-3.63(2H, m), 7.10-7.20(2H, m), 7.35-7.37(1H, m)
4	NMR($CDCl_3$):2.36(3H, s), 2.50-2.70(4H, m), 2.85-2.95(2H, m), 3.13-3.18(2H, m), 7.00(1H, d), 7.23-7.28(1H, m)
5	NMR($CDCl_3$):1.46(9H, s), 2.75-2.85(2H, m), 3.10-3.15(2H, m), 3.45-3.60(4H, m), 6.56(1H, d), 6.82(1H, d)
6	NMR($CDCl_3$):2.23(3H, s)、2.85-2.95(2H, m), 3.10-3.20(2H, m), 3.50-3.60(4H, m), 7.03(1H, d), 7.64(1H, br), 8.10(1H, d)
7	NMR:1.16(6H, t), 3.33-3.41(2H, m), 3.42-3.55(2H, m), 3.60-3.73(4H, m), 4.46(1H, t), 5.68-5.82(1H, brs), 7.16-7.40(3H, m)
8	NMR:3.62(2H, s), 6.21-6.33(2H, m), 6.91-7.00(1H, m), 7.02-7.15(1H, m), 7.68-7.82(1H, brs).
9	NMR:1.14(6H, t), 2.04(1.5H, s), 2.05(1.5H, s), 2.78-3.04(4H, m), 3.45-3.78(8H, m), 3.88-3.95(2H, m), 4.81(1H, t), 6.74-6.81(1H, m), 6.82-6.90(1H, m), 7.03-7.11(1H, s)
10	NMR($CDCl_3$):1.31(3H, t), 1.49(9H, s), 2.77(2H, q), 2.94-3.06(2H, m), 3.16-3.27(2H, m), 3.53-3.68(4H, m), 6.32(1H, s), 6.93(1H, d), 7.19(1H, d)
11	NMR($CDCl_3$):1.19(6H, t), 2.77(2H, d), 2.86-2.98(4H, m), 3.48-3.59(2H, m), 3.64-3.75(2H, m), 3.89(3H, s), 4.60(1H, t), 6.78-6.90(2H, m), 7.15(1H, t)
12	NMR:2.21(3H, s), 2.39-2.42(4H, m), 2.71-2.74(2H, m), 3.00-3.03(2H, m), 5.05-5.07(2H, m), 6.54(1H, d), 6.90(1H, d)
13	NMR:2.23(3H, s), 2.37-2.41(4H, m), 2.65-2.68(4H, m), 5.00-5.03(2H, m), 6.55(1H, s), 6.92(1H, s)
14	NMR:2.24(3H, s), 2.42-2.47(4H, m), 2.88-2.91(2H, m), 3.08-3.11(2H, m), 7.60-7.65(2H, m)
15	NMR($CDCl_3$):2.03-2.15(2H, m), 2.28(3H, s), 2.46(3H, s), 2.60-2.68(2H, m), 2.97(2H, t), 7.52(1H, s)
16	NMR($CDCl_3$):1.20(6H, t), 2.37(3H, s), 2.77(2H, d), 2.84(4H, s), 3.46-3.60(2H, m), 3.63-3.76(2H, m), 4.59(1H, t), 7.02-7.08(2H, m), 7.19-7.26(1H, m)

Table 2

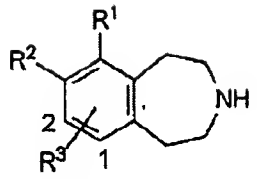
Rf.	Data
17	NMR($CDCl_3$) : 1.23 (3H, t), 2.87 (2H, q), 4.56 (2H, s), 7.23 (1H, t), 7.37 (1H, dd), 7.52 (1H, dd)
18	NMR($CDCl_3$) : 1.30 (2H, br), 2.39 (3H, s), 2.85-3.02 (4H, m), 7.00-7.14 (3H, m)
19	NMR: 2.86-2.94 (2H, m), 3.11-3.19 (2H, m), 3.54-3.67 (4H, m), 4.67-4.81 (2H, m), 7.19 (1H, d), 7.51 (1H, d), 7.70 (1H, d), 7.73 (1H, d)
20	NMR: 1.28 (3H, t), 1.96-2.60 (3H, m), 2.83-3.07 (4H, m), 3.85 (3H, s), 4.17 (2H, q), 6.38 (1H, s)
21a	NMR($CDCl_3$) : 1.48 (9H, s), 2.94-3.04 (2H, m), 3.06-3.15 (2H, m), 3.53- 3.68 (4H, m), 6.73-6.78 (1H, m), 7.06 (1H, d), 7.26 (1H, d), 7.59 (1H, d)
21b	NMR($CDCl_3$) : 1.48 (9H, s), 2.93-3.02 (4H, m), 3.53-3.63 (4H, m), 6.68 (1H, dd), 7.27 (1H, s), 7.33 (1H, s), 7.56 (1H, d)
22	NMR($CDCl_3$) : 2.10 (3H, s), 2.27 (3H, s), 2.53-2.62 (2H, m), 3.14-3.24 (2H, m), 3.54 (2H, s), 7.32 (1H, s).

Table 3



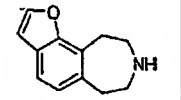
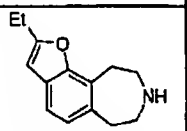
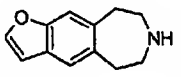
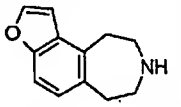
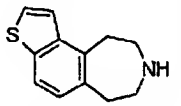
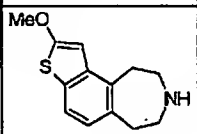
Ex.	R^1	R^2	R^3	Data
1	Cl	NO_2	H	NMR: 3.15-3.35 (6H, m), 3.40-3.50 (2H, m), 7.45 (1H, d), 7.85 (1H, d), 9.63 (2H, br)
2	H	NO_2	2-Cl	NMR: 3.15-3.30 (8H, m), 7.68 (1H, s), 7.99 (1H, s), 9.40-9.70 (2H, br)
3	H	Cl	1-Cl	NMR: 3.10-3.25 (6H, m), 3.30-3.40 (2H, m), 7.35 (1H, d), 7.52 (1H, d), 9.57 (2H, br)
4	Cl	Cl	H	NMR: 3.10-3.22 (6H, m), 3.35-3.44 (2H, m), 7.24 (1H, d), 7.48 (1H, d), 9.51 (2H, br)
5	Cl	NH_2	H	NMR: 3.10 (4H, br), 3.17 (2H, br), 3.32 (2H, br), 6.95-7.10 (2H, m), 7.44 (3H, br), 9.56 (2H, br)
6	Cl	NHAc	H	NMR: 2.08 (3H, s), 3.10-3.25 (6H, m), 3.35-3.45 (2H, m), 7.16 (1H, d), 7.47 (1H, d), 9.45 (2H, br), 9.51 (1H, s)

Table 4



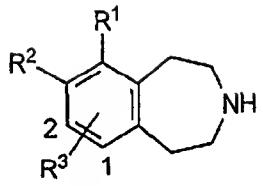
Ex.	R^1	R^2	R^3	Data
7	Cl	$NHSO_2Me$	H	NMR:3.03(3H, s), 3.10-3.25(6H, m), 3.30-3.45(2H, m), 7.20(1H, d), 7.29(1H, d), 9.47(2H, br)
8	Cl	NMeAc	H	NMR:1.66(3H, s), 3.04(3H, s), 3.15-3.30(6H, m), 3.40-3.45(2H, m), 7.31(1H, d), 7.36(1H, d), 9.58(2H, br)
9	Cl	NHMe	H	NMR:2.76(3H, s), 3.00-3.20(6H, m), 3.35-3.40(2H, m), 6.58(1H, d), 6.95(2H, br), 7.04(1H, d), 9.57(2H, br)
10	F	F	H	NMR:3.16(4H, br), 3.20(4H, br), 7.05-7.10(1H, m), 7.15-7.30(1H, m), 9.59(2H, br)
11	Me	F	H	NMR:2.19, (3H, s), 2.20(3H, s), 3.05-3.20(8H, m), 6.90-7.00 (1H, m), 7.00-7.10(1H, m), 9.30-9.65(2H, br)
12	Cl	OMe	H	NMR:3.01-3.50(8H, m), 3.83(3H, s), 6.97(1H, d), 7.16 (1H, d), 9.00-9.29(2H, br)
13	Cl	Br	H	NMR:3.12-3.23(6H, m), 3.42-3.45(2H, m), 7.16(1H, d), 7.60 (1H, d), 9.44(2H, brs)
14	Cl	CN	H	NMR:3.18-3.25(4H, m), 3.29-3.31(2H, m), 3.42-3.44(2H, m), 7.43(1H, d), 7.82(1H, d), 9.69(2H, br)
15	Br	Cl	H	NMR:3.16-3.23(6H, m), 3.40-3.45(2H, m), 7.27(1H, d), 7.43 (1H, d), 9.45(2H, br)
16	Cl	F	H	NMR:3.18-3.20(6H, m), 3.38-3.39(2H, m), 7.24-7.26 (2H, m), 9.61(2H, br)
17	Me	Me	1-Br	NMR:2.16(3H, s), 2.23(3H, s), 3.08-3.17(4H, m), 3.17-3.23 (2H, m), 3.29-3.36(2H, m), 7.35(1H, s), 9.29 (2H, br)
18	Me	Me	H	NMR:2.19(3H, s), 2.23(3H, s), 3.00-3.05(2H, m), 3.08-3.13(6H, m), 6.91(1H, d), 6.96(1H, d), 9.08(2H, br)
19	Me	Cl	H	NMR:2.37(3H, s), 3.02-3.10(2H, m), 3.11-3.20(6H, m), 7.07 (1H, d), 7.25(1H, d), 8.92(2H, br)
20	Et	Cl	H	NMR:1.05(3H, t), 2.82(2H, q), 3.05-3.23(8H, m), 7.08 (1H, d), 7.24(1H, d), 9.38(2H, br)
21	Cl	Me	H	NMR:2.32(3H, s), 3.08-3.23(6H, m), 3.31-3.39(2H, m), 7.10 (1H, d), 7.18(1H, d), 9.20(2H, br)

Table 5

Ex.	Structure	Data
22		NMR:3.18-3.36(6H,m), 3.36-3.50(2H,m), 6.94(1H,d), 7.12 (1H, d), 7.44(1H,d), 7.98(1H,d), 9.64-10.00(2H,br)
23		NMR:1.27(3H,t), 2.78(2H,q), 3.10-3.43(8H,m), 6.56(1H,d), 7.05(1H,d), 7.31(1H,d), 9.03-9.28(2H,br)
24		NMR:3.10-3.28(8H,m), 6.86-6.92(1H,m), 7.43-7.52(2H,m), 7.91-7.98(1H,m), 9.54(2H,br)
25		NMR:3.10-3.42(8H,m), 7.04-7.11(1H,m), 7.16(1H,d), 7.39 (1H, d), 7.94- 8.00(1H,m), 9.52(2H,br)
26		NMR:3.14-3.30(6H,m), 3.48-3.56(2H,m), 7.23(1H,d), 7.62 (1H, d), 7.77(1H,d), 7.81(1H,d), 9.52(2H,brs)
27		NMR:3.10-3.45(8H,m), 3.98(3H,s), 6.78(1H,s), 7.05(1H,d), 7.54 (1H,d), 9.52(2H,br)

In the following, in addition to those described in the examples, the compounds of Table 6 and 7 can be obtained using the preparation methods described above, the preparation methods of reference examples and examples, preparation methods that generally well known to those skilled in the art and modifications thereof, without requiring particular experimentation.

Table 6



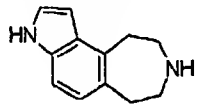
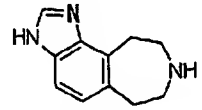
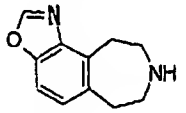
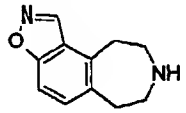
No.	R^1	R^2	R^3
1	Br	F	H
2	I	F	H
3	Et	F	H
4	Pr	F	H
5	iPr	F	H
6	F	Cl	H
7	I	Cl	H
8	CN	Cl	H
9	Pr	Cl	H
10	iPr	Cl	H
11	F	Br	H
12	Br	Br	H
13	I	Br	H
14	CN	Br	H
15	Pr	Br	H
16	iPr	Br	H
17	Me	Br	H
18	Et	Br	H
19	F	I	H
20	Cl	I	H
21	Br	I	H
22	I	I	H
23	CN	I	H
24	Pr	I	H
25	iPr	I	H
26	Me	I	H

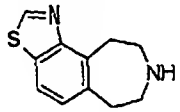
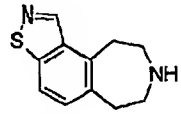
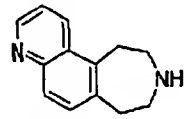
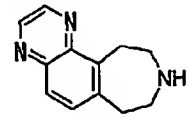
No.	R^1	R^2	R^3
27	Et	I	H
28	F	CN	H
29	Br	CN	H
30	I	CN	H
31	CN	CN	H
32	Pr	CN	H
33	iPr	CN	H
34	Me	CN	H
35	Et	CN	H
36	F	Me	H
37	Br	Me	H
38	I	Me	H
39	CN	Me	H
40	Pr	Me	H
41	iPr	Me	H
42	Et	Me	H
43	F	Et	H
44	Cl	Et	H
45	Br	Et	H
46	I	Et	H
47	CN	Et	H
48	Pr	Et	H
49	iPr	Et	H
50	Me	Et	H
51	Et	Et	H
52	F	Pr	H

No.	R^1	R^2	R^3
53	Cl	Pr	H
54	Br	Pr	H
55	I	Pr	H
56	CN	Pr	H
57	Pr	Pr	H
58	iPr	Pr	H
59	Me	Pr	H
60	Et	Pr	H
61	F	iPr	H
62	Cl	iPr	H
63	Br	iPr	H
64	I	iPr	H
65	CN	iPr	H
66	Pr	iPr	H
67	iPr	iPr	H
68	Me	iPr	H
69	Et	iPr	H
70	H	Cl	2-Cl
71	H	Cl	2-Br
72	H	Br	2-Cl
73	H	Br	2-Br
74	S-Allyl	Cl	H
75	S-Ph	Cl	H
76	O-Ph	Cl	H

Table 7

表 7

No.	Structure
77	
78	
79	
80	

No.	Structure
81	
82	
83	
84	

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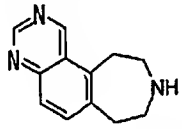
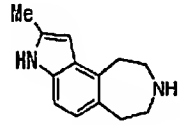
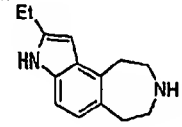
85	
86	
87	

Pharmacological Test Example

In the following, an assay for binding of the compounds (I and II) of the present invention to the 5-HT_{2C} receptor and an animal experiment using rats will be described in detail.

Example 28

Assay for binding to the 5-HT_{2C} receptor

The assay for binding to 5-HT_{2C} receptor was carried out by analyzing the binding of [^{3}H]5-HT according to the method of A. Pazos *et al.*, *Eur. J. Pharmacol.*, 106, 539-546 (1985) or S. Havlik and S. J. Peroutka, *Brain Res.*, 584, 191-196 (1992).

The drug concentration that inhibits 50% of receptor-bound ligand [*sic*] (IC_{50} value) was determined using the above-mentioned method, and the Ki value, which represents the affinity for the receptor, was calculated with the following formula: $Ki=IC_{50}/(1+[L]/[Kd])$ ([L]: ligand concentration, [Kd]: dissociation constant). The results are shown in Table 8.

Table 8

5-HT_{2C} receptor binding assay

Test Compound	K_i (nM)
Example 1	14.0
Example 4	8.8
Example 13	2.4
Example 14	5.1
Example 21	2.9
Example 26	5.0
mCPP	16.0

mCPP (1-(m-chlorophenyl)piperazine) was reported to be an a 5-HT_{2C} receptor agonist (*Life Science*, 43,1297 (1993) and the like).

Example 29

Animal experiment using rats: rat penile erectile initiation action

Induction of penile erection by 5-HT_{2C} receptor stimulation and a test method therefor have been reported (Berendsen & Broekkamp, *Eur. J. Pharmacol.*, 135, 179-184 (1987)).

Following the above-mentioned test method, test compounds were orally administrated to 5 male Wistar rats; the frequency of penile erection 30 minutes immediately after administration was measured and compared with the vehicle treated group (distilled water administered). The minimum effective dose of test compound to observe a statistically significant reaction was determined from the comparative results.

These results are shown in Table 9.

Table 9

Rat penile erectile initiation action (mg/kg, po)

Test compound	Minimum effective dose
Example 4	1.0
Example 13	0.3
Example 14	3.0
Example 21	3.0
mCPP	3.0

Thus, the compounds (I and II) of the present invention included compounds

having affinities for the 5-HT_{2C} receptor that were equal or greater than that of 5-HT_{2C} receptor agonist mCPP. Furthermore, the compounds (I and II) of the present invention were also observed to include compounds having affinities for the 5-HT_{2C} receptor that were equal or greater than that of 5-HT_{2C} receptor agonist mCPP, in terms of rat penile erectile initiation action.

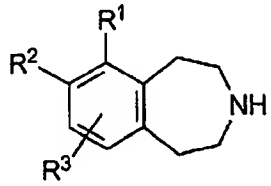
From the foregoing, the compounds (I and II) of the present invention were confirmed to be excellent 5-HT_{2C} receptor agonists.

INDUSTRIAL APPLICABILITY

The compounds (I and II) of the present invention were confirmed to be excellent 5-HT_{2C} receptor agonists by pharmacological tests. Accordingly, the compounds (I and II) of the present invention are useful in the treatment of central nervous system diseases in which the 5-HT_{2C} receptor is involved, such as sexual dysfunction, obesity, hyperphagia, anxiety, depression or sleep disorder.

Claims

1. A 5-HT_{2c} receptor agonist having as effective component a benzoazepine derivative represented by the following Formula (1) or a pharmaceutically acceptable salt thereof.



(I)

(In the Formula, the symbols have the following meanings:

R^1, R^2 and R^3 may be identical or different and represent -H, lower alkyl that may be substituted, lower alkenyl that may be substituted, acyl, -OH, -O-hydrocarbon group that may be substituted, -SH, -S-hydrocarbon group that may be substituted, amino, mono or di-lower alkyl amino, acylamino, a nitrogen of which may be substituted with a lower alkyl, halo, nitro or cyano;

furthermore, R^2 may, together with R^1 or the adjacent R^3, form a heteroaromatic ring that may be substituted.)

2. The 5-HT_{2c} receptor agonist recited in claim 1, wherein R^1 and R^3 are identical or different and represent -H, lower alkyl or halo, and R^2 represents lower alkyl or halo.

3. The 5-HT_{2c} receptor agonist recited in claim 2, wherein R^1 represents halo, R^2 represents lower alkyl or halo and R^3 represents –H.

4. The 5-HT_{2c} receptor agonist recited in claim 3, which is 6,7-dichloro-2,3,4,5-tetrahydro-1H-3-benzoazepine, 7-bromo-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine, 6-chloro-7-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine or pharmaceutically acceptable salts thereof.

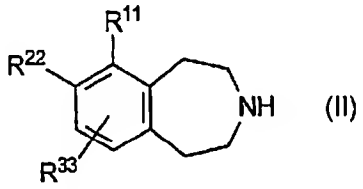
5. The 5-HT_{2c} receptor agonist recited in claim 1, which is a therapeutic agent for sexual dysfunction.

6. The 5-HT_{2c} receptor agonist recited in claim 5, which is a therapeutic agent for erectile insufficiency.

7. Use of the 5-HT_{2c} receptor agonist recited in claim 1 for preparing a therapeutic agent for sexual dysfunction.

8. Therapy for sexual dysfunction comprising administrating to a patient an effective therapeutic dose of the 5-HT_{2c} receptor agonist recited in claim 1.

9. A benzoazepine derivative represented by the following Formula (II), or a pharmaceutically acceptable salt thereof.



(II)

(In the Formula, the symbols have the following meanings:

R^{11} and R^{33}: one of the two represents -H, lower alkyl, amino, mono- or di-lower alkyl amino, acylamino that may have a lower alkyl on the nitrogen, halo, nitro or cyano; the other represents lower alkyl, amino, mono or di-lower alkyl amino, acylamino that may have a lower alkyl on the nitrogen, halo, nitro or cyano;

R^{22} represents a lower alkyl, -OH, -O-lower alkyl, amino, mono- or di-lower alkyl amino, acylamino, a nitrogen of which may be substituted by a lower alkyl, halo, nitro or cyano;

furthermore, R^{22} may, together with R^{11} or the adjacent R^{33}, form a heteroaromatic ring that may be substituted with lower alkyl, -OH or -O-lower alkyl;

however:

1) if R^{11} represents halo and R^{22} represents amino, R^{33} represents a group other than halo;

2) if R^{22} represents -OH or methoxy, R^{11} and R^{33} are identical or different and represent a group other than -OH, methoxy, bromo or nitro; and

3) if R^{11} represents chloro, R^{22} represents a group other than chloro)

10. The compound recited in claim 9, wherein one among R^{11} and R^{33} represents -H, lower alkyl or halo, the other represents lower alkyl or halo, and R^{22} represents lower alkyl or halo.

11. The compound recited in claim 10, wherein R^{11} represents halo, R^{22} represents lower alkyl or halo, and R^{33} represents –H.

12. The compound recited in claim 11, which is 7-bromo-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine or 6-chloro-7-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine, or a pharmaceutically acceptable salt thereof.

13. A medicinal composition comprising the compound recited in claim 9 and a pharmaceutically acceptable carrier.

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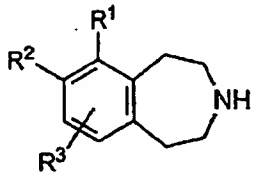
[Title of the Invention] Benzoazepine derivatives

[Claims]

[Claim 1] A 5-HT_{2c} agonist having as effective component a benzoazepine derivative represented by the following Formula (1), or a pharmaceutically acceptable salt thereof.

[Chem. 1]



(I)

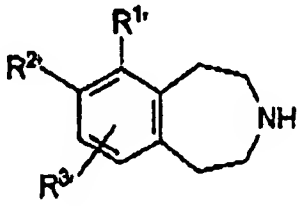
(In the Formula, the symbols have the following meanings:

R^1, R^2 and R^3: may be identical or different and represent -H, lower alkyl that may be substituted, lower alkenyl that may be substituted, -OH, -O-hydrocarbon group that may be substituted, -SH, -S-hydrocarbon group that may be substituted, amino, mono- or di-lower alkyl amino, acylamino, a nitrogen of which may be substituted with a lower alkyl, halo, nitro or cyano;

furthermore, R^2 may, together with R^1 or the adjacent R^3, form a heteroaromatic ring that may be substituted.)

[Claim 2] A benzoazepine derivative represented by the following Formula (II), or a pharmaceutically acceptable salt thereof.

[Chem. 2]



(II)

(In the Formula, the symbols have the following meanings:

$R^{1'}$ and $R^{3'}$: may be the same or different and represent -H, lower alkyl, amino, mono- or di-lower alkyl amino, acylamino that may have a lower alkyl on the nitrogen, halo, nitro or cyano;

$R^{2'}$: represents a lower alkyl, -OH, -O-lower alkyl, amino, mono- or di-lower alkyl amino, acylamino, a nitrogen of which may be substituted by a lower alkyl, halo, nitro or

cyano;

furthermore, $R^{2'}$ may, together with R^1 or the adjacent $R^{3'}$, form a heteroaromatic ring that may be substituted;

however:

1) either one of $R^{1'}$ and $R^{3'}$ represents a group other than –H; and

2) if $R^{1'}$ represents halo and $R^{2'}$ represents amino, $R^{3'}$ represents a group other than halo; if $R^{2'}$ represents -OH or methoxy, $R^{1'}$ and $R^{3'}$ are identical or different and represent a group other than bromo or nitro; and if $R^{1'}$ represents chloro, $R^{2'}$ represents a group other than chloro)

[Detailed Description of the Invention]

[0001]

[Technical Field of the Invention]

The present invention relates to 5-HT_{2c} agonist having a benzoazepine derivative, or a pharmaceutically acceptable salt thereof, as effective component.

Furthermore, the present invention relates to novel benzoazepine derivatives, or pharmaceutically acceptable salts thereof.

[0002]

[Prior Art]

The serotonin 2c (5-HT_{2c}) receptor is distributed mainly in the central nervous system, and although its role has not been enough clarified, it is believed to be involved in central nervous system disease such as sexual dysfunction, appetite regulatory disorders, anxiety, depression and sleep disorder (*Curr. Opin. Invest. Drugs* 2 (4) 317 (1993)). Therefore, a 5-HT_{2c} receptor agonist is useful in the prophylaxis or the treatment of the above-mentioned diseases; and it may, in particular, be useful for patients who have been, up to the present time, excluded from [a diagnosis of] diseases such as sexual dysfunction, and for whom no effective therapy is available.

Tricyclic pyrroles or pyrazole derivatives (EP 657426, EP 700905, WO 98/56768 and the like), tetrahydropyrazinoquinoxaline derivatives (WO 00/35922) or tetracyclic gamma carboline derivatives (WO 00/77001 and the like) and the like have been reported as 5-HT_{2c} receptor agonists.

[0003]

Meanwhile, numerous compounds have been reported as benzoazepine derivatives (EP 285287, EP 589973, EP0229510, US 3716639 and the like) but benzoazepine derivatives having 5-HT_{2c} receptor agonist activity are not know to date.

[0004]

[Problems to Be Solved by the Invention]

An object of the present invention is to provide a 5-HT_{2c} agonist having a benzoazepine derivative, or a pharmaceutically acceptable salt thereof, as effective component.

A further object of the present invention is to provide novel benzoazepine derivatives, or pharmaceutically acceptable salts thereof.

[0005]

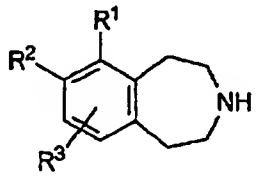
[Means for Solving the Problems]

The present inventors have earnestly investigated 5-HT_{2c} agonists. As a result, they discovered that benzoazepine derivatives represented by the following Formula (I) had a strong agonist activity on the 5-HT_{2c} receptor, and that among the compounds represented by Formula (I), the compound represented by the following Formula (II) was a novel compound, and had an excellent agonist activity on the 5-HT_{2c} receptor; and [in this manner] the present invention was completed.

[0006]

That is to say, the present invention relates to a 5-HL_{2c} agonist having as effective component the zenzazepine [*sic*] derivative represented by the following Formula (I) or a pharmaceutically acceptable salt thereof.

[Chem. 3]



(I)

(In the Formula, the symbols have the following meanings:

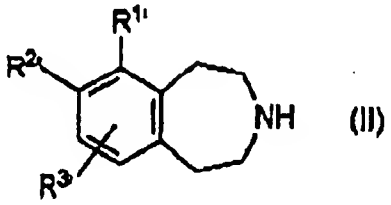
R^1, R^2 and R^3: may be identical or different and represent -H, lower alkyl that may be substituted, lower alkenyl that may be substituted, -OH, -O-hydrocarbon group that may be substituted, -SH, -S-hydrocarbon group that may be substituted, amino, mono- or di-lower alkyl amino, acylamino, a nitrogen of which may be substituted with a lower alkyl, halo, nitro or cyano; furthermore, R^2 may, together with R^1 or the adjacent R^3, form a heteroaromatic ring that may be substituted.)

[0007]

Furthermore the present invention relates to the benzoazepine derivative

represented by the following Formula (II), or a pharmaceutically acceptable salt thereof.

[Chem. 4]



(II)

(In the Formula, the symbols have the following meanings:

$R^{1'}$ and $R^{3'}$: may be the same or different and represent -H, lower alkyl, amino, mono- or di-lower alkyl amino, acylamino that may have a lower alkyl on the nitrogen, halo, nitro or cyano;

$R^{2'}$: represents a lower alkyl, -OH, -O-lower alkyl, amino, mono- or di-lower alkyl amino, acylamino, a nitrogen of which may be substituted by a lower alkyl, halo, nitro or cyano;

furthermore, $R^{2'}$ may, together with R^1 or the adjacent $R^{3'}$, form a heteroaromatic ring that may be substituted;

however:

1) either one of $R^{1'}$ and $R^{3'}$ represents a group other than –H; and

2) if $R^{1'}$ represents halo and $R^{2'}$ represents amino, $R^{3'}$ represents a group other than halo; if $R^{2'}$ represents -OH or methoxy, $R^{1'}$ and $R^{3'}$ are identical or different and represent a group other than bromo or nitro; and if $R^{1'}$ represents chloro, $R^{2'}$ represents a group other than chloro)

[0008]

[Modes of Embodiment of the Invention]

In the following, the compounds (I and II) of the present invention will be described in detail.

In the definition of the formulas in the present specification, unless otherwise stated, the term "lower" means a straight or branched carbon chain having 1 to 6 carbons.

Examples of "lower alkyls" include, for instance, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl or isohexyl; preferably methyl or ethyl.

[0009]

Examples of "lower alkenyls" include, for instance, vinyl, 1-propenyl, allyl,

isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-butene-2-yl, 2-methyl-1-propenyl, 3-butene-2-yl, 2-methyl-2-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl or 5-hexenyl, preferably vinyl or allyl.

"Hydrocarbon group" means lower alkyl, lower alkenyl, cycloalkyl, cycloalkenyl or aryl or a group resulting from substitution or condensation therebetween; preferably lower alkyl, cycloalkyl or aryl.

[0010]

"Cycloalkyl" means a saturated mono- to tricyclic aliphatic hydrocarbon ring group having 3 to 14 carbons, and examples include, for instance, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclooctyl, bicyclononyl, bicyclodecanyl, tricycloundecanyl, tricyclododecanyl or tricyclotridecanyl; preferably cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

"Cycloalkenyl" means an unsaturated aliphatic hydrocarbon ring group, obtained by replacing 1 to 3 of any of the single bonds in the above-mentioned cycloalkyl group by double bonds, and examples include, for instance, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl or cyclooctenyl; preferably cyclopentenyl or cyclohexenyl.

[0011]

"Aryl" means a mono- to tricyclic aromatic hydrocarbon ring group having 6 to 14 carbons, and examples include, for instance, phenyl, biphenyl, naphthyl, anthryl or phenanthryl; preferably phenyl or naphthyl.

"Mono- or di-lower alkylamino" means an amino substituted with 1 to 2 of the above-mentioned lower alkyls; preferably, methylamino or ethylamino.

[0012]

"Acyl" means carbonyl or sulfonyl substituted with the above-mentioned lower alkyl, cycloalkyl or aryl; preferably acetyl or methane sulfonyl,.

"Acyl amino" means amino substituted with the above-mentioned acyl; preferably, acetylamino or methanesulfonylamino.

[0013]

Examples of "halo" include fluoro, chloro, bromo or iodo; preferably, chloro or bromo.

"Heteroaromatic ring" means a 5 to 6 membered heteroaromatic ring having respectively 1 to 2 heteroatoms chosen from the group consisting of nitrogen, oxygen and sulphur, examples include pyrrole, imidazole, furan, oxazole, isoxazole, thiophene, thiazole, isothiazole, pyridine, pyridazine or pyrimidine; preferably, furan or thiophene.

[0014]

"May be substituted" means that this may be substituted with 1 to 4 substituents from 1 to 3 species, examples of these substituents including, for instance, lower alkyl, -OH, -O-lower alkyl, -SH, -S-lower alkyl, amino, mono- or di-lower alkyl amino, acyl, -O-acyl, acyl amino, -COOH, -COO-lower alkyl, halo, nitro or cyano.

Depending on the nature of the substituent, optical isomers (optically active substances, diastereomers and the like) or geometric isomers of compounds (I and II) of the present invention exist. Consequently, the compounds (I and II) of the present invention include mixtures or isolates of these optical isomers or geometric isomers.

[0015]

In addition, the compounds (I and II) of the present invention can form an acid addition salt or a salt with a base. Examples include, for instance, acid addition salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid or phosphoric acid, or organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, citric acid, tartaric acid, carbonic acid, picric acid, methanesulfonic acid, ethane sulfonic acid or glutamic acid, and salts with inorganic bases such as sodium, potassium, magnesium, calcium or aluminium, or organic bases such as methylamine, ethylamine, monoethanolamine, diethanolamine, triethanolamine, cyclohexyl amine, lysine or ornithine. In addition, the compounds (I and II) of the present invention or pharmaceutically acceptable salt thereof can form hydrates, solvates with ethanol and the like or polymorphic crystals.

In addition, the compounds (I and II) of the present invention also include all compounds that are metabolized and converted *in vivo* into the compounds (I and II) of the present invention or pharmaceutically acceptable salt thereof, which is to say, prodrugs. Examples of groups that form prodrugs for the compounds (I and II) of the present invention include the groups that are described in *Prog. Med.* 5:2157-2161 (1985), and the groups that are described in "Drug Development" Volume 7, Molecular Design, Hirokawa-Shoten, 163-198 (1990). Specifically, they are groups that can be converted by hydrolysis or solvolysis, or under physiological conditions, into the primary amines or secondary amines, -OH, -COOH [compounds] or the like of the present invention; for example, –OH prodrugs include -OC(O)-lower alkyl that may be substituted, -OC(O)-aryl that may be substituted, -OC(O)-lower alkylene that may be substituted-C(O)OR (R represents -H or lower alkyl; same hereinafter), -OC(O)-lower

alkenylene that may be substituted-C(O)OR, -OC(O)-lower alkylene-O-lower alkylene-C(O)OR, -OC(O)-C(O)OR, -OC(O)-lower alkenylene that may be substituted-$S(O)_2OR$, -O-phthalidyl, 5-methyl-1,3-dioxolene-2-one-4-yl-methyl oxy and the like.

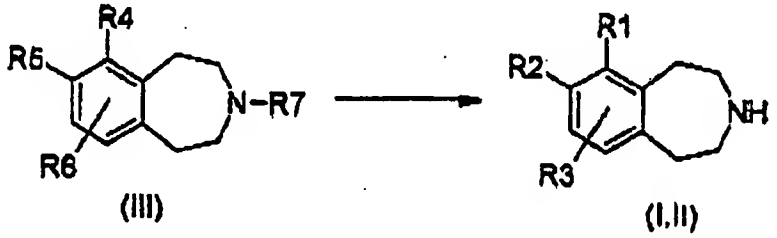
[0016]

Preparation Method

The compounds (I and II) of the present invention can be prepared by applying a variety of synthesis methods, by exploiting characteristics based on the fundamental backbone thereof or the type of substituent. In the following, representative preparation methods will be described.

Preparation 1

[Chem. 5]



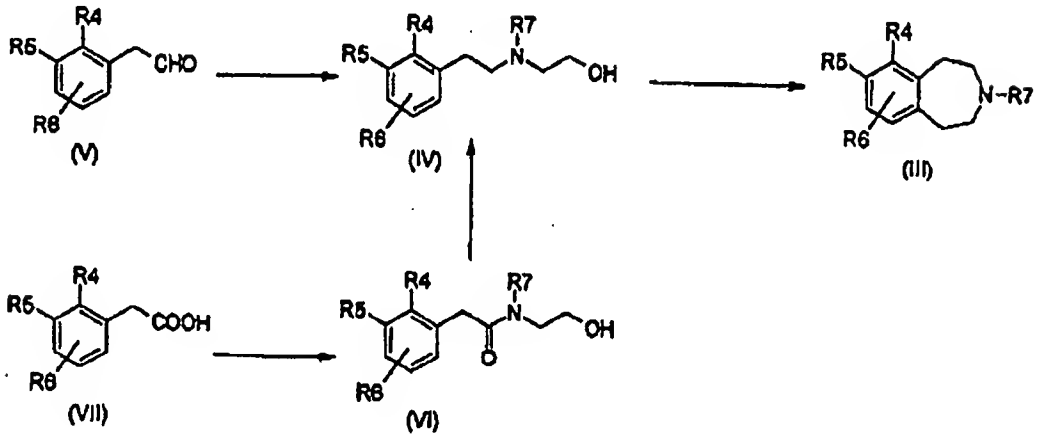
(In the formula, R^1, R^2 and R^3 have the meanings as described above. R^4, R^5 and R^6 respectively mean R^1, R^2 and R^3 or substituents that can be converted into R^1, R^2 and R^3 by a conventional chemical reaction. R^7 means -H or a nitrogen protecting group; Same hereinafter.)

The compounds (I and II) of the present invention can be prepared, if necessary, by converting the functional groups R^4, R^5 and R^6 of compound (III) so as to convert them to R^1, R^2 and R^3, respectively. For instance, in the case of a nitro group, this can be easily converted into chloro, bromo or cyano group or the like by reduction and reversion to amino, followed by the use of a Sandmaeyer reaction (*Org. Syn.* III. 185). In addition, in the case of an amino, the substituent can be easily converted by acylation, alkylation or the like. If R^7 is a protecting group, the desired compounds (I and II) of the present invention can be prepared by deprotection (*Protective group in Organic Synthesis*, Second Ed., JOHN WILEY & SONS, INC.). When R^1 and R^2 together form a furan ring, the compounds (I and II) of the present invention can be prepared from a compound wherein R^4 represents methoxy, according to the synthesis method described in *Synth. Comm.*, 257 (1989) or the like.

Synthesis of the Starting Material

The source compound (III) in Preparation 1 can be prepared according to the following method.

[Chem. 6]



The source compound (III) for the compounds (I and II) of the present invention can be prepared according to the synthesis method described in *J. Med. Chem.*, 26, 1213 (1983). The compound (III) can be prepared, by deriving an amide compound (VI) from a phenylacetic acid derivative (VII) according to a method of the art, further reducing to form a substituted amino ethanol compound (IV), converting the resulting hydroxyl group into a leaving group such as chloro group, and carrying out an intramolecular Friedel-Craft reaction in the presence of a suitable Lewis acid, such as aluminum chloride. In addition, the compound (IV) can also be prepared by a reductive amination reaction of the corresponding aldehyde derivative (V).

[0017]

Preparation 2

[Chem. 7]

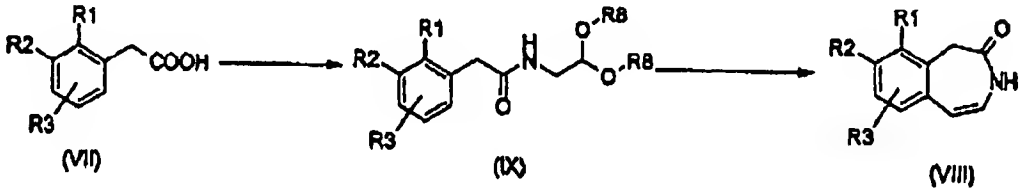
The compounds (I and II) of the present invention can be prepared by reducing compound (VIII).

Preparation is possible by reduction of the olefin portion of compound (VIII); by contact hydrogenation using, for instance, a metal catalyst such as palladium carbon, with acetic acid or ethanol, a mixed solvent thereof or the like as solvent, at ice-cold to room temperature, and reducing the amide portion using, for instance, a reducing agent such as borane or aluminium lithium hydride, with tetrahydrofuran, dioxane or the like as solvent, at ice-cold to room temperature.

Synthesis of the Starting Material

The source compound (VIII) of Preparation 2 can be prepared according to the following method.

[Chem. 8]



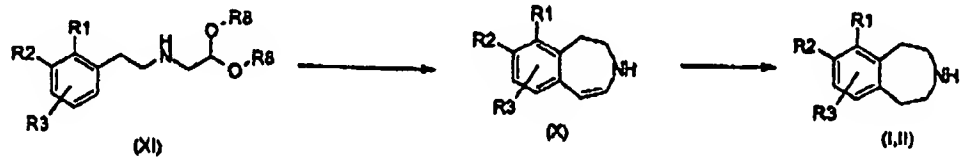
(In the formula, R^8 represents a lower alkyl. Same hereinafter.)

The compound (VIII) can be prepared by adapting the synthesis method described in Japanese unexamined patent application JP-63-255226-A for the compound (VII). The compound (VIII) can be prepared by deriving an amide compound (IX) from the compound (VII) by a method of the art, and reacting under suitable acidic conditions with, for example, sulfuric acid, trifluoromethanesulfonic acid or the like as solvent.

[0018]

Preparation 3

[Chem. 9]



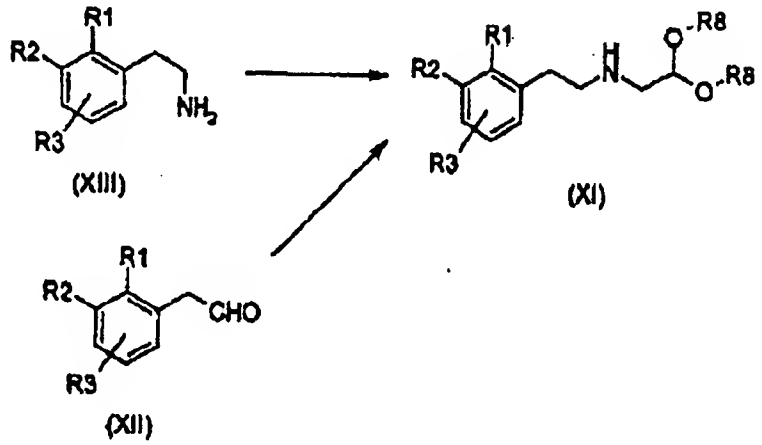
The compounds (I and II) of the present invention can be prepared by reacting a compound (XI) under suitable acidic conditions with, for example, sulfuric acid or trifluoromethanesulfonic acid as solvent, at ice-cold to room temperature, and reducing the olefin portion of the compound (X) that is obtained, in the same manner as in

Preparation 2.

Synthesis of the Starting Material

The source compound (XI) of Preparation 3 can be prepared according to the following method.

[Chem. 10]

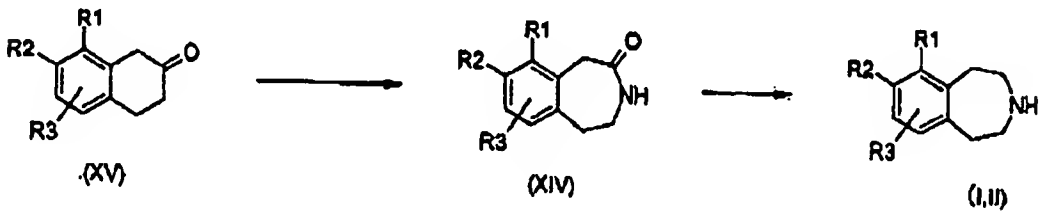


The compound (XI) can be prepared by adapting the synthesis method described in Japanese unexamined patent application JP-55-108855-A for a compound (XIII). The aminoacetaldehyde dialkylacetal compound (XI) can be prepared by methods of the art from the phenethylamine derivative (XIII). Furthermore, compound (XI) can also be prepared by a reductive amination reaction of the like with the corresponding aldehyde compound (XII). The aldehyde compound (XII) can, for example, be prepared by the method described in US 493347.

[0019]

Preparation 4

[Chem. 11]



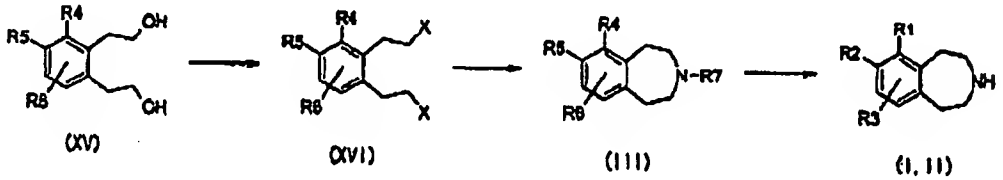
The compounds (I and II) of the present invention can be prepared by carrying out

a Beckmann rearrangement reaction on a β-tetralone derivative (XV) and reducing the obtained amide compound (XIV) in the same manner as in Preparation 2. The Beckmann rearrangement reaction can be carried out with chloroform or methylene chloride or the like as a solvent, in the presence of a suitable acid, such as, in the presence of sulfuric acid, trifluoromethanesulfonic acid or the like, at ice-cold to room temperature. The starting material β-tetralone derivative (XV) can be prepared by the synthesis method described in *Indian J. Chem.*, Sect. B: Org. Chem. Incl. Med. Chem., 37B (3), 281 (1998) or the like.

[0020]

Preparation 5

[Chem. 12]

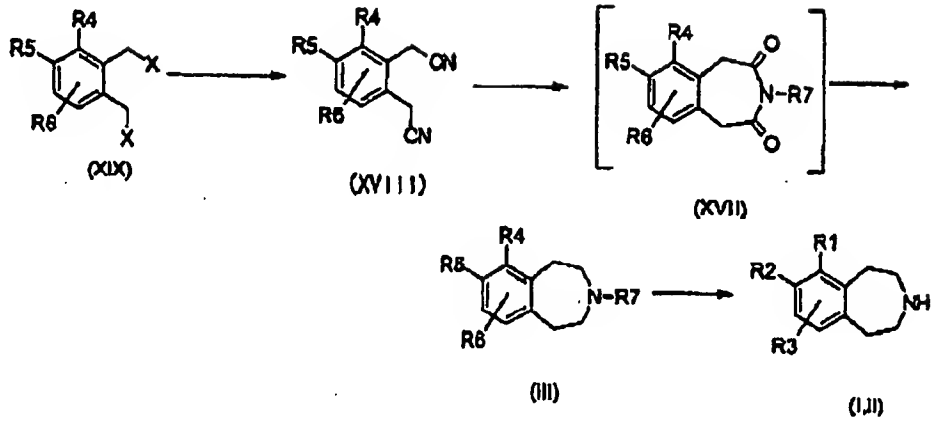


(In the formula, X means tosyloxy, mesyloxy, halo or the like. Same hereinafter.) The compounds (I and II) of the present invention can be prepared according to the synthesis method described in *J. Org. Chem.*, 56, 2937 (1991) or the like; the compounds (I and II) of the present invention can be prepared by the action of a suitable amine on a compound (XVI), which can be prepared from 1,2-bis (hydroxyethyl) benzene derivative (XV), to prepare compound (III), and subsequently following the method of Preparation 1.

[0021]

Preparation 6

[Chem. 13]



The compounds (I and II) of the present invention can be prepared according to the synthesis method described in *J. Med. Chem.*, 27, 918 (1984). They can be prepared from a compound (XIX) having a desired substituent by deriving a cyano compound (XVIII) therefrom following a method of the art, subjecting this to an intramolecular cyclization reaction in the presence of a suitable acid and, passing through compound (XVII), applying reducing conditions. In addition, the compounds (I and II) of the present invention can be prepared by directly applying intramolecular cyclization conditions to the cyano compound (XVIII) in a reductive manner, so as prepare compound (III), and subsequently following Preparation Method 1.

The compounds (I and II) of the present invention prepared in this manner are isolated either in free form, or as salts thereof. A salt of a compound of the present invention can be prepared by subjecting the compound of the present invention in free base form to a conventional salt formation reaction.

Furthermore, the compounds (I and II) of the present invention or salts thereof are isolated and purified as hydrates thereof, solvates thereof, or polymorphic crystalline substances. The isolation and purification are carried out by applying conventional chemical procedures such as extraction, concentration, evaporation, crystallization, filtration, recrystallization, and various types of chromatography.

The various isomers can be separated by selecting a suitable source compound, or exploiting the differences in physical properties between the isomers. For instance, stereochemically pure isomers can be derived from optical isomers by selecting a

suitable starting material, or by a method for resolving a racemic compound (for instance, a method for deriving diastereomeric salts of a common optically active acid, and optically resolving this, or the like).

[0022]

[Examples]

In the following, the present invention will be described in more detail by way of examples; however, the present invention is not limited to these examples.

Preparation Examples

In the following, methods for preparing the compounds (I and II) of the present invention will be described in detail. Note that the source compounds used in the examples are described as reference examples.

Reference Example 1

To a methylene chloride solution (400 ml) of 12.0 of 2,3-dichlorobenzene acetaldehyde, 14. 27 g of 2-(methylamino)ethanol and 40.26 g of sodium triacetoxyborohydride were added, and this was stirred for 4 hours at room temperature. The reaction solution was dumped into aqueous sodium bicarbonate and extracted with chloroform. After combining the organic layers and washing with water and saturated saline, this was dried with anhydrous magnesium sulphate. The solvent was removed by evaporation *in vacuo*, and the residue was purified using silica gel column chromatography (eluant – chloroform : methanol : ammonia water = 100 : 1 : 0.1 to 20 : 1 : 0.1) to produce 13.03 g of 2-[[2-(2,3-dichlorophenyl)ethyl]methylamino]ethanol as a light-yellow oily substance.

[0023]

Reference Example 2

Phosphorus pentachloride in the amount of 2.3 g was added to a 1,2,4-trichlorobenzene solution (25 ml) of 5.34 g of 2-[[2-(2,3-dichlorophenyl)ethyl]methylamino]ethanol, and this was stirred for 1 hour at 100°C. Next, 8.4 g of aluminium chloride were added, and this was stirred for 5 hours at 200°C. To the reaction solution, which had cooled to room temperature, were added 50 ml of 3 mol/L aqueous hydrochloric acid, and the organic layer was separated. The separated aqueous layer was alkalinized using a 50% solution of sodium hydroxide, and extracted using ether. After combining the organic layers and washing with water and saturated saline, this was dried with anhydrous magnesium sulphate. The solvent was removed by evaporation *in vacuo*, and the residue was purified using silica gel column

chromatography (eluant – chloroform : methanol : ammonia water = 100 : 1 : 0.1 to 10 : 1 : 0.1) to produce 1.91 g of 6,7-dichloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine.

[0024]

Reference Example 3

2,4-dichlorophenyl acetic acid was dissolved in 9 ml of thionyl chloride and stirred for 1 hour at 55°C. The solvent was removed by evaporation *in vacuo*; the residue was dissolved in 60 ml of chloroform, a chloroform solution (60 ml) of 9.2 ml of 2-(methylamino) ethanol and 5.3 ml triethilamine was added, and this was stirred at room temperature for 3 hours. The reaction solution was dumped into ice water and extracted using chloroform. After combining the organic layers and washing with 0.5 mol/L aqueous hydrochloric acid, this was dried with anhydrous magnesium sulphate. The solvent was removed by evaporation *in vacuo*, and the residue was washed using hexane to produce 14.62 g of an amide compound as white solids. To the resulting amide compound was added a 1 mol/L solution of borane-tetrahydrofuran (150 ml); and this was stirred for 4 hours at room temperature. After adding 10 ml of methanol to the reaction solution, 50 ml of 6 mol/L aqueous hydrochloric acid was added and this was refluxed for 2 hours. After cooling the reaction solution, the solvent was removed by evaporation *in vacuo*, 100 ml of water were added to the resulting residue; this was further alkalinized using a 50% solution of sodium hydroxide, and extracted using chloroform. The organic layers were combined and dried using anhydrous magnesium sulphate and the solvent was removed by evaporation *in vacuo* to produce 10.66 g of 2-[[2-(2,4-dichlorophenyl)ethyl]methylamino]ethanol as a colorless oily substance.

Reference Example 4

6,8-dichloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine was obtained by a method similar to that in Reference Example 2.

[0025]

Reference Example 5

To a mixture of 0.95 g of the 6-chloro-7-nitro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride obtained in Example 1 and 15 ml of ethyl acetate, were added 0.82 g of di-tert-butyl dicarbonate and 0.53 ml of trimethylamine; and this was stirred at room temperature for 5 hours. To the reaction solution were added 50 ml of water; this was extracted with ethyl acetate (50 ml (1)2); the eluent was washed with a 5%

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[1] *Throughout the Japanese document, it seems that the character "x" has been accidentally replaced by the character "(" –trans.*

aqueous solution of sodium hydrogen sulfate, water and saturated saline and, after drying with anhydrous magnesium sulphate, the solvent was removed by evaporation *in vacuo*. The residue was washed with n-hexane to produce 1.01 g of cream colored solids. To a mixture of 0.63 g of the solid produced above, 2 ml of ethanol, 4 ml of 1,4-dioxane, 3 ml of water, 0.56 g of iron powder and 0.53 g of ammonium chloride were added, and this was stirred overnight at room temperature. Insoluble substances in the reaction solution were removed, the insoluble substances were washed with ethanol and the solvent in the filtrate was removed by evaporation *in vacuo*. The residue was purified by a silica gel column chromatography (ethyl acetate : n-hexane = 1 : 15 to 1 : 5) to produce 0.35 g of 3-(tert-butoxycarbonyl)-7-amino-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine as light yellow solids.

[0026]

Reference Example 6

To a mixture of 0.35 g of the compound produced in Reference Example 5, triethyl amine in the amount of 0.17 ml and 4 ml of tetrahydrofuran, were added 0.09 ml of acetyl chloride, on ice, and this was stirred at room temperature for 5 hours. Ethyl acetate in the amount of 50 ml was added to the reaction solution; this was washed with water and saturated saline and dried with anhydrous sodium sulfate, whereafter the solvent was removed by evaporation *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 5 to 1 : 3) to produce 0.33 g of 3-Boc-7-acetylamino-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine as a viscous colorless oily substance. Note that Boc means t-butoxycarbonyl. Same hereinafter.

[0027]

Reference Example 7

To a dimethyl formamide solution (50 ml) of 4.3 g of 2,3-difluorophenylacetic acid, were added 4 ml of aminoacetaldehyde diethylacetal, 4.21 g of 1-hydroxybenzotriazole and 5.27 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, on ice. After stirring at room temperature for eight hours this was dumped into an aqueous solution of 5% citric acid and extracted using ethyl acetate. After combining the organic layers and washing using water and saturated saline, this was dried with anhydrous sodium sulfate. The solvent was removed by evaporation *in vacuo* and the residue was purified by silica gel column chromatography (eluent - hexane : ethyl acetate = 10 : 1 to 2 : 1) to produce 4.38 g of N-(diethoxyethyl)-2,3-difluorobenzene acetamide as a colorless oily substance.

[0028]

Reference Example 8

N-(diethoxyethyl)-2,3-difluorobenzene acetamide in the amount of 2.38 g was dissolved in 17 ml of concentrated sulfuric acid; 1.5 ml of trifluoromethane sulfonic acid was added, and this was stirred for four hours at 75°C. The reaction solution was dumped into ice water and extracted using ethyl acetate. After combining the organic layers and washing using water and saturated saline, this was dried with anhydrous sodium sulfate. The solvent was removed by evaporation *in vacuo* and the residue was purified using silica gel column chromatography (eluent - hexane : ethyl acetate = 5 : 1 to 2 : 1) to produce 235 mg of 1,3-dihydro-8,9-difluoro-2H-3-benzoazepine-2-one as white solids.

[0029]

Reference Example 9

A mixture of 10.5 g of 3-fluoro-2- methylbenzoic acid and 15 ml of thionyl chloride was stirred for four hours at 60°, whereafter the reaction solution was concentrated *in vacuo*. The residue was dissolved in a mixture of 100 ml of toluene and 10 ml of water, and after adding 0.22 g of tetrabutylammonium hydrogen sulfate, the reaction solution was cooled and 2.6 g of sodium borohydride was gradually added over two hours under ice cold conditions; and this was stirred overnight at room temperature. An amount of 100 ml of saturated sodium hydrogen carbonate was added to the reaction solution; the organic layer was separated; the aqueous layer was extracted with 50 ml of ethyl acetate and combined with the organic layer; this was washed with water and saturated saline; and after drying with anhydrous sodium sulfate, the solvent was removed by evaporation *in vacuo*. The residue was dissolved in 70 ml of tetrahydrofuran; 2.6 g of sodium borohydride, 2.9 g of lithium chloride and 140 ml of ethanol were added; and this was stirred overnight at room temperature. The reaction solution was concentrated *in vacuo* and 200 ml of water and 100 ml of 10% citric acid were added to the concentrate; this was extracted with ethyl acetate (100 ml (2); the eluate was washed with, a saturated aqueous solution of sodium hydrogen carbonate, water and saturated saline, and dried with anhydrous sodium sulfate, whereafter the solvent was removed by evaporation *in vacuo*. The residue was purified using silica gel column chromatography (ethyl acetate : n-hexane = 1 : 50 to 1 : 5) to produce 3.08 g of 3-fluoro-2-methylphenyl methanol as white solids.

[0030]

Reference Example 10

A mixture of 3.06 g of 3-fluoro-2-methylphenyl methanol, 15 ml of 48% hydrobromic acid and 30 ml of toluene was stirred for four hours at 95°C. The reaction solution was allowed to cool, whereafter 50 ml of ethyl acetate were added; this was washed with water and saturated saline, and after drying with anhydrous sodium sulfate, the solvent was removed by evaporation *in vacuo*. The residue was dissolved in 30 ml of ethanol and this was slowly added to a mixture of 1.56 g of potassium cyanide, 0.15 g of tetrabutylammonium hydrogen sulfate and 30 ml of water, and this was stirred for three hours at 50°C. The reaction solution was concentrated *in vacuo*; 50 ml of water were added to the concentrate; this was extracted with ethyl acetate (100 ml (2); the extract was washed with water and saturated saline and dried with anhydrous sodium sulfate, whereafter the solvent was removed by evaporation *in vacuo*. The residue was purified using silica gel column chromatography (ethyl acetate : n-hexane = 1 : 50 to 1 : 20) to produce 2.75 g of white solids. To a mixture of 2.71 g of the white solids produced above and 22 ml of water, were added 18 ml of concentrated sulfuric acid, and this was stirred for four hours under hot reflux. Water in the amount of 50 ml was added to the reaction solution; this was cooled; and the crystals that precipitated were filtered and dried to produce 2.9 g of 3-fluoro-2-methylphenyl acetic acid as white solids.

[0031]

Reference Example 11

6-methoxy-2,3,4,5-tetrahydro-1H-3-benzoazepine in the amount of 1.87 g was dissolved in 48% hydrobromic acid, and this was reacted for three hours at 100°C. After cooling to room temperature, the solvent was removed by evaporation *in vacuo* to produce 6-hydroxy-2,3,4,5-tetrahydro-1H-3-benzoazepine as a semi-purified substance. To a methylene chloride solution thereof, 2 ml of anhydrous acetic acid and 4 ml of triethylamine were added, and this was stirred for two hours at room temperature. The reaction solution was dumped into cooled 1 mol/L aqueous hydrochloric acid; the organic layer and aqueous layer were separated; and the aqueous layer was washed using ether. The organic layer was combined; this was washed using water and saturated saline, and dried with anhydrous magnesium sulfate. After removing the solvent by evaporation, the residue was dissolved in a 1 mol/L aqueous solution of sodium hydroxide; and this was stirred for one hour at room temperature. The reaction solution was acidified by adding a small amount of concentrated hydrochloric acid, and extracted with ethyl acetate. The organic layers were combined, washed using water and saturated saline, and dried with anhydrous magnesium sulfate. The solvent was

removed by evaporation *in vacuo* to produce 1.89 g of 3-acetyl-6-hydroxy-2,3,4,5-tetrahydro-1H-3-benzoazepine as a light yellow solids. This was dissolved in 20 ml of dm; 0.58 g of sodium hydride (60% oil dispersion) were added, on ice, and after stirring for 30 minutes at room temperature, 2.59 g of bromo amino acetaldehyde diethylacetal were added, and this was stirred for one hour at 160° C. The reaction solution was dumped into cooled 1 mol/L aqueous hydrochloric acid; the organic layer and the aqueous layer were separated, and the aqueous layer was washed using ethyl acetate. The organic layer was combined and washed using water and saturated saline, and dried with anhydrous magnesium sulfate. After removing the solvent by evaporation, the residue was purified using silica gel column chromatography (eluent – toluene : ethyl acetate = 2 : 1 to 1: 3) to produce 2.48 g of 3-acetyl-6-(2,2-diethoxyethoxy)-2,3,4,5-tetrahydro-1H-3-benzoazepine.

[0032]

Reference Example 12

To a tetrahydrofuran solution (10 ml) of 0.48 g of 7,8,9,10-tetrahydro-6H-furo[2,3-g][3]benzoazepine, was added 1.11 g of di-tert-butyl dicarbonate, and this was stirred overnight at room temperature. After removing the solvent by way of evaporation *in vacuo*, the residue was purified using silica gel column chromatography (eluent - hexane : ethyl acetate = 10 : 1) to produce 0.78 g of N-Boc-7,8,9,10-tetrahydro-6H-furo[2,3-g][3]benzoazepine. This was dissolved in 10 ml of tetrahydrofuran and after adding n-butyl lithium at -78°C, 0.50 g of ethyl iodide was added. After stirring for 30 minutes at -78°C, the reaction solution was returned to room temperature, stirred for a further 30 minutes, and added to cooled saturated aqueous ammonium chloride. After separating the organic layer, the aqueous layer was extracted with ethyl acetate and combined with the organic layer; and after washing using water and saturated saline, this was dried with anhydrous magnesium sulfate. After removing the solvent by evaporation, the residue was purified by silica gel column chromatography (eluent - hexane : ethyl acetate = 6 : 1) to produce a mixture of source material and the ethyl [derivative]. The resulting mixture was dissolved in 10 ml of tetrahydrofuran and after adding n-butyl lithium at -78° C, 0.37 g of dimethylformamide were added. The reaction solution was returned to room temperature, stirred for one hour, and added to cooled saturated aqueous ammonium chloride. After separating the organic layer, the aqueous layer was washed with ethyl acetate and combined with the organic layer; this was washed using water and saturated saline; then this was dried with anhydrous

magnesium sulfate. After removing the solvent by evaporation, the residue was purified by silica gel column chromatography (eluent – hexane : ethyl acetate = 4 : 1 to 3 : 1) to produce 48 mg of 2-ethyl-N-Boc-7,8,9,10-tetrahydro-6H-furo[2,3-g][3]benzoazepine.

[0033]

Reference Example 13

2-(2-chloro-3-methoxyphenyl)ethyl amine in the amount of 2.10 g was dissolved in 40 ml of dimethylformamide; 7.80 g of potassium carbonate and 2.29 g of bromo acetaldehyde were added, and this was stirred for six hours at 5°C. After cooling the reaction solution, this was dumped into ice water and extracted using ethyl acetate. The organic layers were combined and washed with water and saturated saline, whereafter this was dried with anhydrous magnesium sulfate. After removing the solvent by evaporation, the residue was purified by silica gel column chromatography (eluent – chloroform : methanol = 10 : 1) to produce 1.53 g of [2-(2-chloro-3-methoxyphenyl)ethyl]aminoacetaldehyde diethylacetal as a light yellow oily substance.

[0034]

Reference Example 14

To an acetic acid solution (20 ml) of 2.09 g of 6-chloro-3-methyl-7-nitro-2,3,4,5-tetrahydro-1H-3-benzoazepine, was added 2.42 g of iron powder and this was stirred for two hours at 70°C. After cooling the reaction solution, this was diluted with ethyl acetate; and after removing the insoluble substances, the solvent was removed by evaporation *in vacuo*. After treating the remaining acetic acid by adding saturated aqueous sodium bicarbonate, this was extracted using chloroform and dried with anhydrous sodium sulfate. After removing the solvent by evaporation *in vacuo*, the residue was purified by silica gel column chromatography (eluent – chloroform : methanol : saturated ammonia water = 95 : 5 : 0.5) to produce 1.62 g of 7-amino-6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine as light brown solids.

[0035]

Reference example 15

Using a method similar to that in Reference Example 14, an amount of 4.23 g of 8-amino-7-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine was produced as yellow solids from 6.31 g of 7-chloro-3-methyl-8-nitro-2,3,4,5-tetrahydro-1H-3-benzoazepine.

Reference example 16

A concentrated sulfuric acid solution (10 ml) of 1.00 g of 8-amino-7-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine was cooled to -5 °C, and after instilling

0.33 ml of concentrated nitric acid, this was stirred for four hours. The reaction solution was dumped into ice water and after alkalinization with saturated aqueous ammonia, this was extracted with chloroform and dried with anhydrous sodium sulfate. After removing the solvent by evaporation *in vacuo*, the residue was purified with silica gel column chromatography (eluent – chloroform : methanol : saturated ammonia water = 98 : 2 : 0.2) to produce 0.15 g of 8-amino-7-chloro-3-methyl-6-nitro-2,3,4,5-tetrahydro-1H-3-benzoazepine as yellow solids. This was dissolved in 3 ml of a mixed solution of acetic acid: concentrated sulfuric acid = 1 : 2, and, under ice cold conditions, 0.06 g of sodium nitrite were gradually added, whereafter this was stirred for 30 minutes. This reaction solution was instilled into an aqueous solution (2 ml) of 0.43 g of sodium hypophosphite and 0.46 g of cupric oxide, whereafter this was subject to hot reflux for four hours. The reaction solution was cooled and then dumped into ice water, and after alkalinization with saturated aqueous ammonia, this was extracted using chloroform and dried with anhydrous sodium sulfate. After removing the solvent by evaporation *in vacuo*, the residue was purified by silica gel column chromatography (eluent – chloroform : methanol : saturated ammonia water = 97 : 3 : 0.3) to produce 0.09 g of 7-chloro-3-methyl-6-nitro-2,3,4,5-tetrahydro-1H-3-benzoazepine as a colorless oily substance.

[0036]

Reference Example 17

4-bromo-1,2-dimethyl benzene was dissolved in 140 ml of dichloromethane, and after adding 4.16 g of succinic anhydride, 11.1 g of aluminum chloride were added under ice cold conditions, and this was stirred overnight at room temperature. The reaction solution was dumped into cooled aqueous hydrochloric acid; the organic layer and aqueous layer were separated, and the aqueous layer was washed using chloroform. The organic layer was combined, washed using saturated saline, dried with anhydrous magnesium sulfate, and after removing the solvent by evaporation, the residue was purified by silica gel column chromatography (eluent – chloroform : methanol = 50 : 1) to produce 11.46 g of a mixture of 3-(2-bromo-4,5-dimethyl benzoyl) propionic acid and 3-(5-bromo-2,3-dimethyl benzoyl) propionic acid. An amount of 10.74 g of this mixture was dissolved in 75 ml of diethylene glycol; 7.46 g of potassium hydroxide and 5.48 ml of hydrazine hydrate were added and this was stirred for two hours at 120°C, and two and half hours at 210°C. After returning the reaction solution to room temperature, 150 ml of water were added; and after washing with diethyl ether, 1N aqueous hydrochloric acid was added so as to acidify it, and this was extracted with diethyl ether. The organic

layers were combined; after washing with saturated saline, this was dried with anhydrous sodium sulfate, and the solvent was removed by evaporation to produce 7.88 g of a mixture of 4-(2-bromo-4,5-dimethylphenyl)butanic acid and 4-(5-bromo-2,3-dimethylphenyl)butanic acid. This mixture was dissolved in 50 ml of acetic anhydride; 3 ml of 85% phosphoric acid were added; and this was stirred for 30 minutes at room temperature. After removing the solvent by evaporation, 300 ml of hexane were added this was washed with saturated aqueous sodium bicarbonate and saturated saline, and dried with anhydrous sodium sulfate, whereafter the solvent was removed by evaporation. The residue was purified by silica gel column chromatography (eluent - hexane : ethyl acetate = 20 : 1 to 15 : 1), whereafter the resulting coarse product was dissolved in 70 ml of trifluoroacetic acid; 8.16 ml of anhydrous trifluoroacetic acid were added, and this was stirred overnight at room temperature. After removing the solvent by evaporation, 300 ml of hexane were added, and this was washed with water, saturated aqueous sodium bicarbonate and saturated saline, and dried with anhydrous sodium sulfate, whereafter the solvent was removed by evaporation, and the residue was purified by silica gel column chromatography (eluent - hexane : ethyl acetate = 100 : 1) to produce 1.75 g of 5-bromo-7,8-dimethyl-3,4-dihydro-1(2H)-naphthalenone as light yellow solids.

[0037]

Reference Example 18

After dissolving 713 mg of sodium hydroxide in 1.7 ml of water, to the solution to which 160 mg of sodium borohydride had been added, 7 ml of methanol and 14 ml a dichloromethane solution of 3.30 g of 2-chloro-1-(3-chloro-2-methylphenyl) ethanone were successively instilled while stirring on ice, whereafter this was stirred overnight at room temperature. Water in the amount of 100 ml was added to the reaction solution; and after neutralization with 1N aqueous hydrochloric acid, this was extracted with chloroform; after washing the combined organic layers with saturated saline, this was dried with anhydrous sodium sulfate; and the solvent was removed by evaporation to produce 1.72 g of 3-chloro-2-methylstyrene oxide as a coarse product. A 20 ml benzene solution of this product was added to a 70 ml of a benzene solution of 1.56 g of zinc iodide and stirred for 40 minutes at room temperature. After adding hexane, the solution was washed with water, saturated aqueous sodium bicarbonate and saturated saline, whereafter this was dried with anhydrous sodium sulfate; the solvent was removed by evaporation and the residue was purified by silica gel column chromatography (eluent -

hexane : ethyl acetate = 30 : 1) to produce 1.07 g of (3-chloro-2-methylphenyl) acetaldehyde as a colorless oily substance. The resulting aldehyde was dissolved in 10 ml of 1,2-dichloroethane; 4.61 ml of aminoacetaldehyde diethylacetal and 2.42 ml of acetic acid were added; this was stirred for 45 minutes at room temperature; and after adding 20 ml of 1,2-dichloroethane, 1.75 g of triacetoxy sodium borohydride were added, and this was stirred overnight at room temperature. Saturated aqueous sodium bicarbonate was added to the reaction solution; this was extracted with chloroform; and after washing the combined organic layers with saturated saline, this was dried with anhydrous sodium sulfate, the solvent was removed by evaporation, and the residue was purified by silica gel column chromatography (eluent – chloroform : ethanol = 100 : 0 to 100 : 1) to produce 591 mg of 2-(3-chloro-2-methylphenyl)ethyl]aminoacetaldehyde diethylacetal as a yellow oily substance.

[0038]

Reference Example 19

1,3-dichloro-2-ethyl benzene in the amount of 6.74 g, 992 mg of magnesium and 100 µL of 1,2-dibromoethane were subjected to hot reflux in tetrahydrofuran, to prepare a solution of (3-chloro-2-ethylphenyl)magnesium-tetrahydrofuran chloride. This was instilled under ice cold conditions to a 40 ml toluene/80 ml tetrahydrofuran solution of 4.06 g of 2-chloro-N-methoxy-N-methyl acetamide and stirred for one and half hours at room temperature. The reaction solution was dumped into 1N aqueous hydrochloric acid; the organic layer was extracted; and after washing with saturated saline, this was dried with anhydrous sodium sulfate; the solvent was removed by evaporation; and the residue was purified by silica gel column chromatography (eluent - hexane : ethyl acetate = 40 : 1) to produce 1.98 g of 2-chloro-1-(3-chloro-2-ethylphenyl)ethanone as colorless solids.

[0039]

Reference Example 20

To a 60 ml of tetrahydrofuran suspension of 3.72 g of aluminium lithium hydride, was added 30 ml of a tetrahydrofuran solution of 5.20 g of 2-chloro-3-methylbenzene acetonitrile, and this was stirred overnight at room temperature. To the reaction solution was added 3.72 ml of water, 3.72 ml of a 15% aqueous solution of sodium hydroxide, and 11.2 ml of water; following Celite filtration, the solvent was removed by evaporation and the residue was purified by silica gel column chromatography (eluent – chloroform : methanol = 20 : 1 to 5 : 1) to produce 2.71 g of 2-chloro-3-methylbenzene ethanamine

as a light yellow oily substance.

[0040]

Reference Example 21

To a mixture of 1.48 g of sodium hydride and 70 ml of tetrahydrofuran, were instilled 7.32 ml of ethyl diethylphosphonoacetate, on ice; and after stirring for 30 minutes, a mixture of 2.93 g of 4,5,6,7-tetrahydro-4-oxobenzo[b]thiophene-5-acetic ethyl ester and 30 ml of tetrahydrofuran was added, and this was subject to hot reflux for 40 hours. After cooling the reaction solution, this was poured into a saturated aqueous solution of ammonium chloride, and extracted using diethyl ether. The organic layer was washed using saturated saline; after drying with magnesium sulfate, the solvent was removed by evaporation, and the residue was purified by silica gel column chromatography (eluent - ethyl acetate : hexane = 1 : 20) to produce 2.26 g of ethyl 5-ethoxycarbonylmethyl-6,7-dihydro-5H-benzo[b]thiophene-4-ylidene acetic ester. Ethyl 5-ethoxycarbonylmethyl-6,7-dihydro-5H-benzo[b]thiophene-4-ylidene acetic ester in the amount of 2.15 g was dissolved in 20 ml of diethylene glycol diethyl ether; 2.15 g of 10% palladium carbon were added; this was stirred for 30 minutes at 100°C, and a further one hour at 150°C in an argon atmosphere. After cooling the reaction solution, Celite was used for filtering and that Celite was washed with ethyl acetate. After concentrating the filtrate *in vacuo*, the residue was purified by silica gel column chromatography (eluent - ethyl acetate : hexane = 1 : 20) to produce 1.50 g of 4,5-bis(ethoxycarbonylmethyl)benzo[b]thiophene. To a mixture of 733 mg of aluminium lithium hydride and 150 ml of tetrahydrofuran, was instilled a mixture of 1.48 g of 4,5-bis(ethoxycarbonylmethyl)benzo[b]thiophene and 20 ml of tetrahydrofuran, on ice, and this was stirred at room temperature for two hours. After adding 100 ml of tetrahydrofuran to the reaction solution, 3 ml of methanol, 0.8 ml of water, and 0.8 m of a 1N aqueous solution of sodium hydroxide were successively added, and this was stirred for one hour at room temperature. The reaction solution was filtered using Celite, and after concentrating the filtrate *in vacuo*, the residue was purified by silica gel column chromatography (eluent – chloroform : methanol = 20 : 1) to produce 0.72 g of 4,5-bis(2-hydroxyethyl)benzo[b]thiophene.

[0041]

Reference Example 22

To a mixture of 11.1 ml of N,N-diisopropylamine and 200 ml of tetrahydrofuran, were instilled 45.2 ml of a 1.6 M butyl lithium hexane solution, on ice, and this was

stirred for 30 minutes. The reaction solution was cooled to -78°; a mixed solution of 12.0 g of 2-methoxy-6,7-dihydrobenzothiophene-4(5H)-one and 100 ml of tetrahydrofuran was instilled; after stirring for one hour at the same temperature, 9.49 ml of ethyl bromoacetate was added; and this was warmed to room temperature and stirred for a further 10 hours. The reaction solution was poured into saturated saline and extracted using ethyl acetate. After drying the organic layer with magnesium sulfate, the solvent was removed by evaporation and the residue was purified by silica gel column chromatography (eluent – ethyl acetate : hexane = 1 : 9) to produce 9.75 g of 2-methoxy-4,5,6,7-tetrahydro-4-oxobenzo[b]thiophene-5-acetic acid ethyl ester.

[0042]

Reference Example 23

To a mixture of 4.72 g of sodium hydroxide and 100 ml of N-dimethylformamide, were instilled 10.0 g of 3,4-dimethylphenol, on ice, and after stirring for 30 minutes at the same temperature, 14.8 ml of bromoacetaldehyde diethylacetal were added, and this was stirred for five hours at 170°. After cooling the reaction solution to room temperature, the excess sodium hydroxide was treated with methanol, and this was poured into ice water. This was extracted using ethyl acetate and successively washed with a 1N aqueous solution of sodium hydroxide and saturated saline. After drying the organic layer with magnesium sulfate, the solvent was removed by evaporation and the residue was purified by silica gel column chromatography (eluent – ethyl acetate : hexane = 1 : 10) to produce 14.3 g of 3,4-dimethyl-1-(2,2-diethoxyethoxy)benzene.

[0043]

Reference Example 24

3,4-dimethyl-1-(2,2-diethoxyethoxy)benzene in the amount of 14.2 g was dissolved in 250 ml of benzene, and after adding 14.2 ml of polyphosphoric acid, this was stirred for 30 minutes. The benzene phase of the reaction solution was separated from the polyphosphoric acid phase, and after diluting the benzene phase in diethyl ether, this was successively washed with water, saturated aqueous sodium bicarbonate.and saturated saline. The organic layer was dried with magnesium sulfate, whereafter the solvent was removed by evaporation and the residue was purified by silica gel column chromatography (eluent – hexane) to produce 5.10 g of a mixture of 4,5-dimethylbenzofuran and 5,6-dimethyl benzofuran. An amount of 5.10 g of a mixture of 4,5-dimethylbenzofuran and 5,6-dimethyl benzofuran was dissolved in 150 ml of carbon tetrachloride; 12.4 g of N-bromosuccinic imide and 100 mg of 2,2'-azobisisobutyronitrile

were added, and this was subject to hot reflux for four hours. The reaction solution was cooled to room temperature, and after filtering using Celite, the solvent was removed by evaporation, and the residue was purified by silica gel column chromatography (eluent – hexane) to produce 4.60 g of a mixture of 4,5-bis bromomethylbenzofuran and 5,6-bis bromomethylbenzofuran. An amount of 4.60 g of this mixture of 4,5-bis bromomethylbenzofuran and 5,6-bis bromomethylbenzofuran was dissolved in 50 ml of dimethyl sulfide, 2.22 g of sodium cyanide was slowly added, and this was stirred at room temperature for one hour. The reaction solution was poured into water and extracted using ethyl acetate, and washed with saturated saline. After drying the organic layer with magnesium sulfate, the solvent was removed by evaporation and the residue was purified by silica gel column chromatography (eluent – ethyl acetate : hexane = 1 : 4) to produce 1.44 g of a mixture of 4,5-bis cyanomethylbenzofuran and 5,6-bis cyanomethylbenzofuran. An amount of 1.44 g of this mixture of 4,5- bis cyanomethylbenzofuran and 5,6- bis cyanomethylbenzofuran was dissolved in 6 ml of acetic acid; 12 g of a 33% solution of hydrobromic acid, acetic acid was instilled and this was stirred for a further two hours at room temperature. After removing the solvent from the reaction solution *in vacuo*, 40 ml of water and 2.00 g of sodium acetate were added, and this was subject to hot reflux for four hours. The reaction solution was cooled to room temperature, and the crystals that precipitated were recovered by filtration and dried. These crystals were dissolved in 20 ml of tetrahydrofuran; 1.76 ml of a 10M borane-dimethyl sulfide complex were added and this was stirred at room temperature for 12 hours. The reaction solution was cooled to ice cold, and after adding 5 ml of concentrated hydrochloric acid, this was stirred for two hours at room temperature. The reaction solution was poured into water, neutralized using a 30% aqueous solution of sodium hydrochloride, and extracted using chloroform. After drying the organic layer with magnesium sulfate, the solvent was removed by evaporation, and the residue was purified by silica gel column chromatography (eluent – chloroform : methanol : saturated ammonia water = 100 : 10 : 1) to produce 0.41 g of a mixture of 6,7,8,9-tetrahydro-5H-furo[2,3-h][3]benzoazepine and 7,8,9,10-tetrahydro-6H-furo[3,2-g][3]b benzoazepine. An amount of 400 mg of this mixture of 6,7,8,9-tetrahydro-5H-furo[2,3-h][3]benzoazepine and 7,8,9,10-tetrahydro-6H-furo[3,2-g][3]b benzoazepine was dissolved in 20 ml of tetrahydrofuran, 930 mg of di-t-butyl dicarbonate were added and it was stirred at room temperature for one hour. After removing the solvent by evaporation *in vacuo*, the residue was purified by silica gel column chromatography (eluent – ethyl acetate :

hexane = 1 : 20) to produce 284 mg of 7-Boc-6,7,8,9-tetrahydro-5H-furo[2,3-h][3]benzoazepine (24a) and 120 mg of 8-Boc-7,8,9,10-tetrahydro-6H-furo[3,2-g][3]b benzoazepine (24b).

[0044]

Reference Example 25

5-bromo-7,8-dimethyl-3,4-dihydro-1(2H)-naphthalenone in the amount of 1.74 g was dissolved in 50 ml of methanol; and after adding 520 mg of sodium borohydride, this was stirred overnight at room temperature. After removing the solvent by evaporation, 100 ml of saturated aqueous sodium bicarbonate were added; this was extracted with ethyl acetate; the combined organic layers were washed with saturated saline, whereafter this was dried with anhydrous sodium sulfate; the solvent was removed by evaporation, and the residue was purified by silica gel column chromatography (eluent – hexane : ethyl acetate = 40 : 1 to 5 : 1) to produce 1.51 g of 5-bromo-7,8-dimethyl-1,2,3,4-tetrahydro-1-naphthol as colorless solids. An amount of 1.21 g of the substance was dissolved in 40 ml of benzene, 95 mg of p-toluene sulfonate-hydrate were added, and this was subjected to hot reflux for two hours. After cooling the reaction solution, 60 ml of hexane were added, and this was washed with saturated aqueous sodium bicarbonate and saturated saline, whereafter this was dried with anhydrous sodium sulfate; and the solvent was removed by evaporation to produce 1.13 g of 8-bromo-5,6-dimethyl-1,2-dihydronaphthalene. The substance was dissolved in 30 ml of dichloromethane; 1.14 g of m-chloroperoxybenzoic acid were added; and this was stirred overnight at 4°C. Dichloromethane in the amount of 70 ml was added to the reaction solution; this was washed with saturated aqueous sodium bicarbonate and saturated saline; and after drying with anhydrous sodium sulfate, the solvent was removed by evaporation to produce 1.58 g of 5-bromo-7,8-dimethyl-1,2,3,4-tetrahydro-1,2-epoxynaphthalene. The substance was dissolved in 50 ml of benzene; 721 µL of trifluoroboron-diethyl ether complex were added; and this was stirred for one and half hours at room temperature. Hexane was added to the reaction solution, this was washed with water, saturated aqueous sodium bicarbonate and saturated saline, and dried with anhydrous sodium sulfate, whereafter the solvent was removed by evaporation and the residue was purified by silica gel column chromatography (eluent – hexane : ethyl acetate = 10 : 1) to produce 0.79 g of 5-bromo-7,8-dimethyl-3,4-dihydro-2(1H)-naphthalenone as colorless solids.

[0045]

Example 1

To a mixed solution of 2.04 g of 6-chloro-3-methyl-7-nitro-2,3,4,5-tetrahydro-1H-3-benzoazepine and 17 ml of 1,2-dichloro ethane, 1 ml of 1-chloroethyl chloroformate was added, and the solution was stirred overnight under heated reflux. The solvent of the reaction solution was removed by evaporation *in vacuo*, 15 ml of methanol was added to the residue, which was stirred for 5 hours under heated reflux, and then the solvent was removed by evaporation *in vacuo*. Water and a saturated aqueous solution of sodium hydrogen carbonate, in the amounts of 50 ml each, were added to the residue, which was extracted with chloroform (50 ml (2); and after the extract was dried with anhydrous sodium sulfate, the solvent was removed by evaporation *in vacuo*. The residue was purified by silica gel column chromatography (chloroform : methanol : concentrated ammonia water = 100 : 1 : 0.1 to 30 : 1 : 0.1) to obtain 1.06 g of a colorless oily substance. The oily substance obtained above was dissolved in 20 ml of ethyl acetate, 1.5 ml of 4 mol/L hydrochloric acid-ethyl acetate was added, and the deposited insoluble matter was collected by filtration to obtain 1.2 g of 6-chloro-7-nitro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride as a white solid.

The compounds of Example 2 to 4 were obtained by a method similar to that in Example 1.

Example 2: 7-chloro-8-nitro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride

Example 3: 6,8-dichloro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride

Example 4: 6,7-dichloro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride

[0046]

Example 5

A solution of 4 mol/L hydrochloric acid-ethyl acetate in the amount of 0.5 ml was added to a mixed solution of 90 mg of 3-Boc-7-amino-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine obtained in Reference Example 5, 2 ml of ethyl acetate and 1 ml of methanol, and this was stirred for 2 hours at room temperature. The solvent of the reaction solution was removed by evaporation *in vacuo* and the residue was washed with ethyl acetate to obtain 80 mg of 7-amino-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride as a white solid.

Example 6

7-acetyl amino-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained by a method similar to that in Example 5.

[0047]

Example 7

Methane sulfonyl chloride in the amount of 0.05 ml was added to a mixed solution of 0.18 g of 3-Boc-7-amino-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine, 0.09 ml of triethylamine and 2 ml of 1,2-dichloroethane on ice, and this was stirred overnight at room temperature. A saturated aqueous solution of sodium hydrogencarbonate in the amount of 30 ml was added to the reaction solution; this was extracted with chloroform (50 ml (2); and after the extract was dried with anhydrous sodium sulfate, the solvent was removed by evaporation *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 5 to 1 : 3) to obtain 85 mg of 3-Boc-6-chloro-7-mesylamino-2,3,4,5-tetrahydro-1H-3-benzoazepine as colorless caramel, and 6-chloro-7-mesylamino-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained by a method similar to that in Example 5.

[0048]

Example 8

On Ice, 30 mg of sodium hydride (60%) and 0.05 ml of methyl iodide were added to a mixed solution of 0.23 g of 3-Boc-7-acetylamino-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine and 3ml of N,N-dimethyl formamide, and this was stirred for 5 hours at room temperature. Ethyl acetate in the amount of 50 ml was added to the reaction solution, which was washed with water and saturated saline and dried with anhydrous sodium sulfate, whereafter the solvent was removed by evaporation *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3 to 1 : 1) to obtain 0.21 g of 3-Boc-6-chloro-7-acetyl methylamino-2,3,4,5-tetrahydro-1H-3-benzoazepine as a colorless non-crystalline powder, and 7-acetyl methylamino-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained by a method similar to that in Example 4.

[0049]

Example 9

After a mixed solution of 100 mg of 7-acetyl methylamino-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine and 2 ml of concentrated hydrochloric acid was stirred for 2 hours at 100°C, the solvent of the reaction solution was removed by evaporation. After the residue was washed with acetonitrile, the crude crystal obtained was dispersed in 30 ml of an aqueous solution of saturated sodium bicarbonate and extracted with ethyl acetate (50 ml (2); and after the extract was washed with water and saturated saline,

and dried with anhydrous sodium sulfate, the solvent was removed by evaporation *in vacuo*. The residue was dissolved in 3 ml of methanol and 3 ml of ethyl acetate, 0.4 ml of 4 mol/L hydrochloric acid-ethyl acetate was added, and the solution was stirred for 1 hour at room temperature, whereafter the solvent was removed by evaporation *in vacuo*. The residue was washed with ethyl acetate to obtain 45 mg of 6-chloro-7-methylamino-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride as a white solid.

[0050]

Example 10

1,3-dihydro-8,9-difluoro-2H-3-benzoazepine-2-one in the amount of 0.26 g was dissolved in 5 ml of acetic acid, to which 50 mg of 10% palladium carbon was added, and the solution was stirred for 5 hours under hydrogen flow. After completion of the reaction, undissolved substances were removed by Celite filtration, and the filtrate was concentrated. A solution of 1 M borane tetrahydrofuran (3.3 ml) was added to this reductant, which was stirred overnight at room temperature. After 2 ml of methanol was added to the reaction solution, 5 ml of 1 mol/L aqueous hydrochloric acid was added and the solution was refluxed for 2 hours. After cooling the reaction solution, the solvent was removed by evaporation *in vacuo*, 15 ml of water and 5 ml of 1 mol/L sodium hydroxide were added to the obtained residue, and then the solution was extracted with chloroform. The organic layers were combined and dried with anhydrous sodium sulfate, whereafter the solvent was removed by evaporation *in vacuo*, and the residue was purified using silica gel column chromatography (eluent – chloroform : methanol : ammonia water = 100 : 1 : 0.1 to 30 : 1 : 0.1) . The purification product obtained was dissolved in 0.5ml of a solution of 4mol/L hydrochloric acid-ethyl acetate and stirred. The precipitate was collected by filtration and dried *in vacuo* to obtain 0.14 g of 6,7-difluoro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride as a white solid.

Example 11

7-fluoro-6-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained by a method similar to that in Example 10.

[0051]

Example 12

On ice, 1.50 g of 2-(2-chloro-3-methoxyphenyl)ethyl]aminoacetaldehyde diethylacetal was added to 10 ml of concentrated sulfuric acid and stirred for 1 hour at room temperature. The reaction solution was dumped into cold water and neutralized by adding an aqueous solution of 2 mol/L sodium hydroxide and extracted using ethyl

acetate. The organic layers were combined, washed using water and saturated saline and then dried with anhydrous magnesium sulfate. After removal of solvent by evaporation, the residue was purified by silica gel column chromatography (eluent – chloroform : methanol = 10 : 1) to obtain 85 mg of 9-chloro-8-methoxy-2,3-dihydro-1H-3-benzoazepine. This was dissolved in a mixed solvent of 2 ml of tetrahydrofuran and 2 ml of 0.5 M sodium dihydrogenphosphate aqueous solution, and 0.25 g of sodium cyanoborohydride was added, and a reaction was carried out for 1 hour at room temperature. Saturated aqueous sodium bicarbonate was added to the reaction solution, chloroform was added, and the organic layer was separated. The aqueous layer was washed using chloroform, and the organic layers were combined and dried with anhydrous magnesium sulfate. After removal of solvent by evaporation, the residue was purified by silica gel column chromatography (eluent – chloroform : methanol = 10 : 1), the pale yellow oily substance that was obtained was dissolved in a solution of 4 mol/L hydrochloric acid-ethyl acetate, and the crystal that precipitated was collected by filtration and dried *in vacuo* to obtain 54 mg of 6-chloro-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride as a white solid.

[0052]

Example 13

An aqueous solution of 47% hydrogen bromide in the amount of 1 ml was added to an aqueous solution (2.5 ml) of 0.40 g of 7-amino-6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine, which was subjected to heated reflux for 20 minutes. The reaction solution was cooled on ice, 0.13 g of sodium nitrite was added in small amounts in such a way that the temperature of the reaction solution did not exceed 10°C, whereafter the solution was stirred for 20 minutes. This reaction solution was instilled to a solution wherein an aqueous solution (2 ml) of 0.33 g of copper (I) bromide and 0.65 ml of a 47% aqueous solution of hydrogen bromide had been mixed on ice, so that the temperature of the reaction solution did not exceed 10°C, then stirred for 2 hours. The reaction solution was dumped into ice water, alkalinized by adding an aqueous solution of 1N sodium hydroxide, then extracted using ethyl acetate and dried with anhydrous sodium sulfate. After removal of solvent by evaporation *in vacuo*, the residue was purified by silica gel column chromatography (eluent – chloroform : methanol : saturated ammonia water = 98 : 2 : 0.2) to obtain 0.16 g of 7-bromo-6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine as a light brown oily substance, and 47 mg of 7-bromo-6-chloro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained as a colorless solid by a

method similar to that in Example 1.

[0053]

Example 14

An amount of 3.13 g of an aqueous solution (9 ml) of potassium cyanide was added to 1.19 g of an aqueous solution (5 ml) of copper (I) chloride, and the solution was stirred for 30 minutes at room temperature, whereafter 32 ml of benzene was added to prepare a solution of copper (I) cyanide. On ice, 0.59 g of sodium nitrite was added in small amounts to 1.20 g of 7-amino-6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine in an aqueous solution of 2N hydrochloric acid (21 ml) so that the temperature of the reaction solution did not exceed 10°C, and then the solution was stirred for 30 minutes. Toluene in the amount of 24 ml was added to this reaction solution, and the aqueous layer was neutralized with sodium carbonate. On ice, this solution was instilled into the solution of copper (I) cyanide that was prepared beforehand in such a way that the temperature of the reaction solution did not exceed 10°C, and then stirred for 30 minutes, returned to room temperature and stirred overnight. After the reaction solution was diluted with ethyl acetate, it was washed using an aqueous solution of 10% sodium carbonate and dried with anhydrous sodium sulfate. After removal of solvent by evaporation *in vacuo*, the residue was purified by silica gel column chromatography (eluent – chloroform : methanol = 97 : 3) to obtain 0.75 g of 6-chloro-7-cyano-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine as a light brown solid, and 428 mg of 6-chloro-7-cyano-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained as a colorless solid by a method similar to that in Example 1.

Example 15

Using a method similar to that in Reference Example 8, 6-amino-7-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine was obtained, and 7-chloro-6-bromo-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained using a method similar to that in Example 13.

[0054]

Example 16

7-amino-6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine in the amount of 0.58 g was dissolved in 1.26 ml of an aqueous solution of 48% tetrafluoroboric acid, 0.19 g of sodium nitrate was added in small amounts on ice, whereafter the solution was stirred for 1 hour. After the water of the reaction solution was removed by evaporation *in vacuo*, the solution was stirred for 3 hours at 160°C. After cooling the reaction solution,

this was diluted with saturated ammonia water, then extracted using chloroform and dried with anhydrous sodium sulfate. After removal of solvent by evaporation *in vacuo*, the residue was purified by silica gel column chromatography (eluent – chloroform : methanol : saturated ammonia water = 97 : 3 : 0.3) to obtain 0.48 g of 6-chloro-7-fluoro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine as a light brown oily substance, and 6-chloro-7-fluoro-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained using a method similar to that in Example 1.

[0055]

Example 17

5-bromo-7,8-dimethyl-3,4-dihydro-2(1H)-naphthalenone in the amount of 0.79 g was dissolved in 45 ml of chloroform, 19 ml of concentrated sulfuric acid was added on ice, the solution was stirred for 5 minutes at room temperature, 406 mg of sodium azide was added over 25 minutes, and then the solution was stirred for 7 hours at room temperature. After dumping the reaction solution on ice and dissolution, the organic layers, which had been extracted with chloroform and combined, were washed with saturated aqueous sodium bicarbonate and saturated saline, whereafter the solution was dried with anhydrous sodium sulfate, and the solvent was removed by evaporation to obtain 718 mg of a mixture of 6-bromo-8,9-dimethyl-2-oxo-2,3,4,5-tetrahydro-1H-3-benzoazepine and 6-bromo-8,9-dimethyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzoazepine. The step described above was repeated once, 816 mg of the mixture obtained was dissolved in 75 ml of tetrahydrofuran, whereafter 1N borane-tetrahydrofuran complex and 15.2 ml of tetrahydrofuran solution were added, and the soution was stirred for 1 hour at room temperature and 2.5 hours at 60°C. After adding 152 ml of 1N aqueous hydrochloric acid to the reaction solution and subjecting this to heated reflux for 40 minutes, the solution was alkalinized with an aqueous solution of 1N sodium hydroxide and the organic layers, which had been extracted with chloroform and combined were washed with saturated saline, then dried with anhydrous sodium sulfate; the solvent was removed by evaporation; the residue was purified by silica gel column chromatography (eluent – chloroform : methanol : concentrated ammonia water = 10 : 1 : 0 to 10 : 1 : 0.1); and the product obtained was treated with a solution of 4N hydrochloric acid-ethyl acetate to obtain 161 mg of 9-bromo-6,7-dimethyl-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride as a colorless solid.

[0056]

Example 18

9-bromo-6,7-dimethyl-2,3,4,5-tetrahydro-1H-3-benzoazepine in the amount of 128 mg was dissolved in 20 ml of ethanol, 20 mg of 10% palladium carbon was added, and the solution was stirred overnight at room temperature under hydrogen at 1 atmosphere. After Celite filtration of the reaction solution, the solvent was removed by evaporation and saturated aqueous sodium bicarbonate was added, whereafter the organic layers that had been extracted with ethyl acetate and combined were washed with saturated saline, and then dried with anhydrous potassium carbonate and the solvent was removed by evaporation. The same reaction procedure was carried out again until disappearance of the starting materials was confirmed; and after Celite filtration of the reaction solution, the solvent was removed by evaporation, the product obtained was treated with a solution of 4 mol/L hydrochloric acid-ethyl acetate, and this was recrystallized from ethanol-diethyl ether to obtain 50 mg of 6,7-dimethyl-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride as a colorless solid.

Example 19

7-chloro-6-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained using a method similar to that in Example 12.

Example 20

7-chloro-6-ethyl-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained using a method similar to that in Reference Example 18 and Example 12.

Example 21

6-chloro-7-methyl-2,3,4,5-tetrahydro-1H-3-benzoazepine hydrochloride was obtained using a method similar to that in Reference Example 13 and Example 12.

[0057]

Example 22

Polyphosphoric acid in the amount of 1.65 g was added to a benzene solution (30 ml) containing 1.65 g of 3-acetyl-6-(2,2-diethoxyethoxy)-2,3,4,5-tetrahydro-1H-3-benzoazepine obtained in Reference Example 11, which was subjected to heated reflux for 30 minutes. After cooling the reaction solution, the organic layer and polyphosphoric acid were separated, the organic layer was diluted with ethyl acetate, washed using water and saturated saline and dried with anhydrous magnesium sulfate. After removal of solvent by evaporation, the residue was purified by silica gel column chromatography (eluent – toluene : ethyl acetate = 1 : 1 to 1 : 3), to obtain a 2:3 mixture of product and starting materials. The mixture obtained was dissolved in 20 ml of methanol, 9 ml of an aqueous solution of 40% potassium hydroxide was added and the reaction was

performed for 4 hours at 70°C. After cooling the reaction solution, this was extracted using chloroform and the organic layers were combined, washed using water and saturated saline, and then dried with anhydrous magnesium sulfate. After removal of solvent by evaporation, the residue was dissolved in tetrahydrofuran, 0.50 g of di-tert-butyl dicarbonate was added, and the solution was stirred for 1 hour at room temperature. After removal of solvent by evaporation, the residue was purified by silica gel column chromatography (eluent – hexane : ethyl acetate = 9 : 1 to 6 : 1) and the product obtained was treated with a solution of 4 mol/L hydrochloric acid-ethyl acetate to obtain 28 mg of 7,8,9,10-tetrahydro-6H-furo[2,3-g][3]benzoazepine hydrochloride as a colorless solid.

The compounds of Examples 23 to 25 were obtained by a method similar to that in Example 5.

Example 23: 2-ethyl-7,8,9,10-tetrahydro-6H-furo[2,3-g][3]benzoazepine hydrochloride

Example 24: 6,7,8,9-tetrahydro-5H-furo[2,3-h][3]benzoazepine hydrochloride

Example 25: 7,8,9,10-tetrahydro-6H-furo[3,2-g][3]b benzoazepine hydrochloride

[0058]

Example 26

After 300 mg of 4,5-bis (2-hydroxyethyl) benzo[b]thiophene was dissolved in 10 ml of tetrahydrofuran and cooled to -20 °C 540 mg of chloro p-toluene sulfonic acid, 393 μl of triethylamine and a catalytic amount of dimethylaminopyridine were added, and the solution was stirred for 113 hours at room temperature. Thereafter, 540 mg of chloro p-toluene sulfonic acid and 393 μl of triethylamine were further added, and the solution was stirred for 24 hours at room temperature. After the reaction solution was filtered and washed with diethyl ether, the filtrate was sequentially washed with an aqueous solution of 10% citric acid, saturated aqueous sodium bicarbonate and saturated saline. After the organic layer was dried with magnesium sulfate, the solvent was removed by evaporation, the residue was purified by silica gel column chromatography (eluent – ethyl acetate : hexane = 1 : 2) and somewhat concentrated, whereafter 30 ml of dioxane was added, and concentration was carried out *in vacuo* until the amount of solvent was about 15 ml. Potassium carbonate in the amount of 3.00 g was added to this solution and a mixed solution of 516 μl of benzylamine and 10 ml of dioxane was instilled over 1 hour under heated reflux. After a further 40 hours of heated reflux, the reaction solution was cooled and filtered. The filtrate was concentrated *in vacuo* and the residue was

purified by silica gel column chromatography (eluent – ethyl acetate : hexane = 1 : 5) to obtain 269 mg of 8-benzyl-7,8,9,10-tetrahydro-6H-thieno[3,2-g][3]benzoazepine, and 7,8,9,10-tetrahydro-6H-thieno[3,2-g][3]benzoazepine hydrochloride was obtained by a method similar to that in Example 1.

Example 27

2-methoxy-7,8,9,10-tetrahydro-6H-thieno[3,2-g][3]benzoazepine hydrochloride was obtained from 2-methoxy-4,5,6,7-tetrahydro-4-oxo benzo[b] thiophene-5-ethyl acetate ester using a method similar to that in Reference Example 17 and Example 26.

[0059]

The structural chemical formulas and the physicochemical characteristics of the compounds obtained in the examples are shown in the following tables.

The symbols in the tables have the following meanings.

Rf.: Reference Example Number

Ex.: Example Number

Ac: acetyl

Me: methyl

Et: ethyl

Pr: propyl

iPr: isopropyl

Allyl: allyl

Ph: phenyl

NMR: nuclear magnetic resonance spectrum (internal reference: DMSO-d_6, TMS, unless otherwise noted) δ:

[0060]

Table 1

Rf.	Data
1	NMR: 2.26 (3H, s), 2.42-2.50 (2H, m), 2.53-2.62 (2H, m), 2.84-2.93 (2H, m), 3.40-3.48 (2H, m), 3.64 (1H, t), 7.28 (1H, dd), 7.36 (1H, dd), 7.48 (1H, dd)
2	NMR: 2.23 (3H, s), 2.42-2.50 (4H, m), 2.87-2.94 (2H, m), 3.11-3.19 (2H, m), 7.14 (1H, d), 7.37 (1H, d)
3	NMR ($CDCl_3$): 2.35 (3H, s), 2.55-2.70 (4H, m), 2.83-2.92 (2H, m), 3.52-3.63 (2H, m), 7.10-7.20 (2H, m), 7.35-7.37 (1H, m)
4	NMR ($CDCl_3$): 2.36 (3H, s), 2.50-2.70 (4H, m), 2.85-2.95 (2H, m), 3.13-3.18 (2H, m), 7.00 (1H, d), 7.23-7.28 (1H, m)
5	NMR ($CDCl_3$): 1.46 (9H, s), 2.75-2.85 (2H, m), 3.10-3.15 (2H, m), 3.45-3.60 (4H, m), 6.56 (1H, d), 6.82 (1H, d)
6	NMR ($CDCl_3$): 2.23 (3H, s). 2.85-2.95 (2H, m), 3.10-3.20 (2H, m), 3.50-3.60 (4H, m), 7.03 (1H, d), 7.64 (1H, br), 8.10 (1H, d)
7	NMR: 1.16 (6H, t), 3.33-3.41 (2H, m), 3.42-3.55 (2H, m), 3.60-3.73 (4H, m), 4.46 (1H, t), 5.68-5.82 (1H, brs), 7.16-7.40 (3H, m)
8	NMR: 3.62 (2H, s), 6.21-6.33 (2H, m), 6.91-7.00 (1H, m), 7.02-7.15 (1H, m), 7.68-7.82 (1H, brs).
9	NMR ($CDCl_3$): 1.64 (1H, t). 2.26 (3H, d). 4.70 (2H, d). 6.95-7.05 (1H, m). 7.10-7.20 (2H, m)
10	NMR ($CDCl_3$): 2.22 (3H, d). 3.68 (2H, s). 6.85-7.30 (3H, m). 9.95 (1H, br)
11	NMR: 1.14 (6H, t), 2.04 (1.5H, s), 2.05 (1.5H, s), 2.78-3.04 (4H, m), 3.45-3.78 (8H, m), 3.88-3.95 (2H, m), 4.81 (1H, t), 6.74-6.81 (1H, m), 6.82-6.90 (1H, m), 7.03-7.11 (1H, s)
12	NMR ($CDCl_3$): 1.31 (3H, t), 1.49 (9H, s), 2.77 (2H, q), 2.94-3.06 (2H, m), 3.16-3.27 (2H, m), 3.53-3.68 (4H, m), 6.32 (1H, s), 6.93 (1H, d), 7.19 (1H, d)
13	NMR ($CDCl_3$): 1.19 (6H, t), 2.77 (2H, d), 2.86-2.98 (4H, m), 3.48-3.59 (2H, m), 3.64-3.75 (2H, m), 3.89 (3H, s), 4.60 (1H, t), 6.78-6.80 (2H, m), 7.15 (1H, t)
14	NMR: 2.21 (3H, s), 2.39-2.42 (4H, m), 2.71-2.74 (2H, m), 3.00-3.03 (2H, m), 5.05-5.07 (2H, m), 6.54 (1H, d), 6.90 (1H, d)
15	NMR: 2.23 (3H, s), 2.37-2.41 (4H, m), 2.65-2.68 (4H, m), 5.00-5.03 (2H, m), 6.55 (1H, s). 6.92 (1H, s)
16	NMR: 22.24 (3H, s), 2.42-2.47 (4H, m), 2.88-2.91 (2H, m), 3.08-3.11 (2H, m), 7.60-7.65 (2H, m)
17	NMR ($CDCl_3$): 2.03-2.15 (2H, m), 2.28 (3H, s), 2.46 (3H, s), 2.60-2.68 (2H, m), 2.97 (2H, t), 7.52 (1H, s)

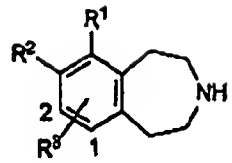
[0061]

Table 2

Rf.	Data
18	NMR ($CDCl_3$): 1.20 (6H, t), 2.37 (3H, s), 2.77 (2H, d), 2.84 (4H, s), 3.46-3.60 (2H, m), 3.63-3.76 (2H, m), 4.59 (1H, t), 7.02-7.08 (2H, m), 7.19-7.26 (1H, m)
19	NMR ($CDCl_3$): 1.23 (3H, t), 2.87 (2H, q), 4.56 (2H, s), 7.23 (1H, t), 7.37 (1H, dd), 7.52 (1H, dd)
20	NMR ($CDCl_3$): 1.30 (2H, br), 2.39 (3H, s), 2.85-3.02 (4H, m), 7.00-7.14 (3H, m)
21	NMR: 2.86-2.94 (2H, m), 3.11-3.19 (2H, m), 3.54-3.67 (4H, m), 4.67-4.81 (2H, m), 7.19 (1H, d), 7.51 (1H, d), 7.70 (1H, d), 7.73 (1H, d)
22	NMR: 1.28 (3H, t), 1.96-2.60 (3H, m), 2.83-3.07 (4H, m), 3.85 (3H, s), 4.17 (2H, q), 6.38 (1H, s)
23	NMR ($CDCl_3$): 1.20-1.30 (6H, m), 2.18 (3H, s), 2.22 (3H, s), 3.57-3.82 (4H, m), 3.97 (2H, d), 4.82 (1H, t), 6.66 (1H, dd), 6.74 (1H, d), 7.01 (1H, d)
24a	NMR ($CDCl_3$): 1.48 (9H, s), 2.94-3.04 (2H, m), 3.06-3.15 (2H, m), 3.53-3.68 (4H, m), 6.73-6.78 (1H, m), 7.06 (1H, d), 7.26 (1H, d), 7.59 (1H, d)
24b	NMR ($CDCl_3$): 1.48 (9H, s), 2.93-3.02 (4H, m), 3.53-3.63 (4H, m), 6.68 (1H, dd), 7.27 (1H, s), 7.33 (1H, s), 7.56 (1H, d)
25	NMR: 2.10 (3H, s), 2.27 (3H, s), 2.53-2.62 (2H, m), 3.14-3.24 (2H, m), 3.54 (2H, s), 7.32 (1H, s).

[0062]

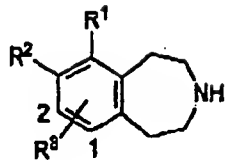
Table 3



Ex.	R^1	R^2	R^3	Data
1	Cl	NO_2	H	NMR:3.15-3.35(6H,m), 3.40-3.50 (2H,m), 7.45(1H,d), 7.85 (1H,d), 9.63(2H,br)
2	H	NO_2	2-Cl	NMR:3.15-3.30(8H,m), 7.68(1H,s), 7.99(1H,s), 9.40-9.70 (2H,br)
3	H	Cl	1-Cl	NMR:3.10-3.25(6H,m), 3.30-3.40(2H,m), 7.35(1H,d), 7.52 (1H,d), 9.57(2H,br)
4	Cl	Cl	H	NMR:3.10-3.22(6H, m), 3.35-3.44(2H, m), 7.24(1H, d), 7.48 (1H, d), 9.51(2H, br)
5	Cl	NH_2	H	NMR:3.10(4H,br), 3.17(2H,br), 3.32(2H,br), 6.95-7.10 (2H,m), 7.44(3H,br), 9.56(2H,br)
6	Cl	NHAc	H	NMR:2.08(3H,s), 3.105-3.25(6H,m), 3.35-3.45(2H,m), 7.16 (1H,d), 7.47(1H,d), 9.45(2H,br), 9.51(1H,s)

[0063]

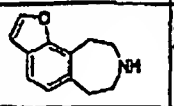
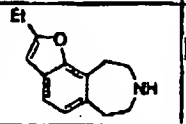
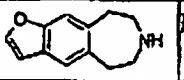
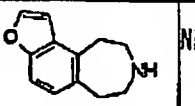
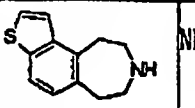
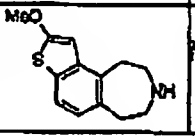
Table 4



Ex.	R^1	R^2	R^3	Data
7	Cl	$NHSO_2Me$	H	NMR:3.03(3H,s), 310-3.25(6H,m), 3.30-3.45(2H,m), 7.20 (1H,d), 7.29(1H,d), 8.47(2H,br)
8	Cl	NMeAc	H	NMR:1.66(3H,s), 3.04(3H,s), 3.15-3.30(6H,m), 3.40-3.45 (2H,m), 7.31(1H,d), 7.36(1H,d), 9.58(2H,br)
9	Cl	NHMe	H	NMR:2.76(3H,s), 3.00-3.20(6H,m), 3.35-3.40(2H,m), 6.58 (1H,d), 6.95(2H,br), 7.04(1H,d), 9.57(2H,br)
10	F	F	H	NMR:3.16(4H,br), 3.20(4H,br), 7.05-7.10(1H,m), 7.15-7.30(1H,m), 9.59(2H,br)
11	Me	F	H	NMR:2.19,(3H,s), 2.20(3H,s), 3.05-3.20(8H,m), 6.90-7.00 (1H,m), 7.00-7.10(1H,m), 9.30-9.65(2H,br)
12	Cl	OMe	H	NMR:3.01-3.50(8H,m), 3.83(3H,s), 6.97(1H,d), 7.16 (1H, d), 9.00-9.29(2H,br)
13	Cl	Br	H	NMR:3.12-3.23(6H,m), 3.42-3.45(2H,m), 7.16(1H,d), 7.60 (1H, d),. 9.44(2H, brs)
14	Cl	CN	H	NMR:3.18-3.25(4H, m), 3.29-3.31(2H, m), 3.42-3.44(2H, m), 7.43(1H, d), 7.82(1H, d), 9.69(2H, br)
15	Br	Cl	H	NMR:3.16-3.23(6H, m), 3.40-3.45(2H, m), 7.27(1H, d), 7.43 (1H, d), 9.45(2H, br)
16	Cl	F	H	NMR:3.18-3.20(6H, m), 3.38-3.39 2H, m), 7.24-7.26 (2H, m), 9.61(2H, br)
17	Me	Me	1-Br	NMR:2.16(3H, s), 2.23(3H, s), 3.08-3.17(4H, m), 3.17-3.23(2H, m), 3.29-3.36(2H, m), 7.35(1H, s), 9.29 (2H, br)
18	Me	Me	H	NMR:2.19(3H, s), 2.23(3H, s), 3.00-3.05(2H, m), 3.08-3.13(6H, m), 6.91(1H, d), 6.96(1H, d), 9.08(2H, br)
19	Me	Cl	H	NMR:2.37(3H, s), 3.02-3.10(2H, m), 3.11-3.20(6H, m), 7.07 (1H, d), 7.25(1H, d), 8.92(2H, br)
20	Et	Cl	H	NMR:1.05(3H, t), 2.82(2H, q), 3.05-3.23(8H, m), 7.08 (1H, d), 7.24(1H, d), 9.38(2H, br)
21	Cl	Me	H	NMR:2.32(3H, s), 3.08-3.23(6H, m), 3.31-3.39(2H, m), 7.10 (1H, d), 7.18(1H, d), 9.20(2H, br)

[0064]

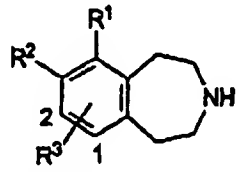
Table 5

Ex.	Structure	Data
22		NMR:3.18-3.36(6H,m), 3.36-3.50(2H,m), 6.94(1H,d), 7.12 (1H, d), 7.44(1H,d), 7.98(1H,d), 9.64-10.00(2H,br)
23		NMR:1.27(3H,t), 2.78(2H,q), 3.10-3.43(8H,m), 6.56(1H,d), 7.05(1H,d), 7.31(1H,d), 9.03-9.28(2H,br)
24		NMR:3.10-3.28(8H,m), 6.86-6.92(1H,m), 7.43-7.52(2H,m), 7.91-7.98(1H,m), 9.54(2H,br)
25		NMR:3.10-3.42(8H,m), 7.04-7.11(1H,m), 7.16(1H,d), 7.39 (1H,d), 7.94- 8.00(1H,m), 9.52(2H,br)
26		NMR:3.14-3.30(6H,m), 3.48-3.56(2H,m), 7.23(1H,d), 7.62 (1H,d), 7.77(1H,d), 7.81(1H,d), 9.52(2H,brs)
27		NMR:3.10-3.45(8H,m), 3.98(3H,s), 6.78(1H,s), 7.05(1H,d), 7.54(1H,d), 9.52(2H,br)

In the following, in addition to those described in the examples, the compounds of Table 6 and 7 can be obtained using the preparation methods described above, the preparation methods of reference examples and examples, preparation methods that generally well known to those skilled in the art and modifications thereof, without requiring particular experimentation.

[0065]

Table 6



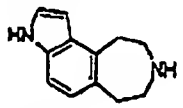
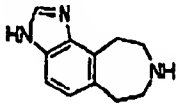
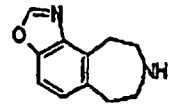
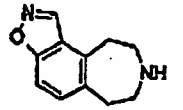
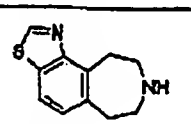
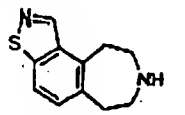
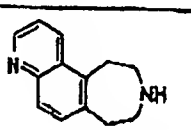
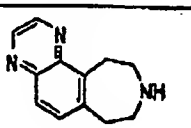
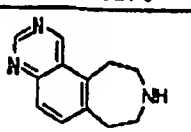
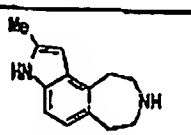
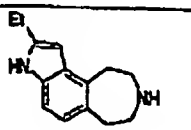
No.	R^1	R^2	R^3
1	Br	F	H
2	I	F	H
3	Et	F	H
4	Pr	F	H
5	iPr	F	H
6	F	Cl	H
7	I	Cl	H
8	CN	Cl	H
9	Pr	Cl	H
10	iPr	Cl	H
11	F	Br	H
12	Br	Br	H
13	I	Br	H
14	CN	Br	H
15	Pr	Br	H
16	iPr	Br	H
17	Me	Br	H
18	Et	Br	H
19	F	I	H
20	Cl	I	H
21	Br	I	H
22	I	I	H
23	CN	I	H
24	Pr	I	H
25	IPr	I	H

No.	R^1	R^2	R^3
26	Me	I	H
27	Et	I	H
28	F	CN	H
29	Br	CN	H
30	I	CN	H
31	CN	CN	H
32	Pr	CN	H
33	iPr	CN	H
34	Me	CN	H
35	Et	CN	H
36	F	Me	H
37	Br	Me	H
38	I	Me	H
39	CN	Me	H
40	Pr	Me	H
41	iPr	Me	H
42	Et	Me	H
43	F	Et	H
44	Cl	Et	H
45	Br	Et	H
46	I	Et	H
47	CN	Et	H
48	Pr	Et	H
49	iPr	Et	H
50	Me	Et	H

No.	R^1	R^2	R^3
51	Et	Et	H
52	F	Pr	H
53	Cl	Pr	H
54	Br	Pr	H
55	I	Pr	H
56	CN	Pr	H
57	Pr	Pr	H
58	iPr	Pr	H
59	Me	Pr	H
60	Et	Pr	H
61	F	iPr	H
62	Cl	iPr	H
63	Br	iPr	H
64	I	iPr	H
65	CN	iPr	H
66	Pr	iPr	H
67	iPr	iPr	H
68	Me	IPr	H
69	Et	IPr	H
70	H	OMe	2-Br
71	SAllyl	Cl	H
72	SAllyl	Cl	H
73	SPh	Cl	H
74	OPh	Cl	H

[0066]

Table 7

No.	Structure
75	
76	
77	
78	
79	
80	
81	
82	
83	
84	
85	

[0067]

Pharmacological Test Example

In the following, an assay for binding of the compounds (I and II) of the present invention to the 5-HT_{2C} receptor and an animal experiment using rats will be described in detail.

Example 29

Assay for binding to the 5-HT_{2C} receptor

The assay for binding to 5-HT_{2C} receptor was carried out by analyzing the binding of [^{3}H]5-HT according to the method of A. Pazos *et al.*, *Eur. J. Pharmacol.*, 106, 539-546 (1985) or S. Havlik and S. J. Peroutka, *Brain Res.*, 584, 191-196 (1992).

The drug concentration that inhibits 50% of receptor-bound ligand [*sic*] (IC_{50} value) was determined using the above-mentioned method, and the Ki value, which represents the affinity for the receptor, was calculated with the following formula: $Ki=IC_{50}/(1+[L]/[Kd])$ ([L]: ligand concentration, [Kd]: dissociation constant).

The results are shown in Table 8.

[0068]

Table 8

Binding Assay Ki (nM)

Test Compound	5-HT_{2C} receptor
Example 4	8.8
Example 13	2.4
Example 21	2.9

[0069]

Example 30

Animal experiment using rats: rat penile erectile initiation action

Induction of penile erection by 5-HT_{2C} receptor stimulation is known (Berendsen & Broekkamp, *Eur. J. Pharmacol.*, 135, 179-184 (1987)).The test compounds were administered to rats and the frequency of penile erection 30 minutes immediately after administration was measured and the minimum effective dose of test compound to observe a statistically significant reaction was determined.

These results are shown in Table 9.

[0070]

Table 9

Rat penile erectile initiation action (mg/kg, sc)

Test compound	Minimum effective dose
Example 4	0.3
Example 13	0.1 to 0.3
Example 21	1 to 3

[0071]

[Effect of the Invention]

The compounds (I and II) of the present invention were found to have high affinities for the 5-HT_{2C} receptor. Furthermore, the compounds (I and II) of the present invention were effective in tests for evaluation of improvement in sexual function, using rats, and were found to be excellent 5-HT_{2C} agonists.

Thus the compounds (I and II) of the present invention have excellent 5-HT_{2C} agonist activity and are also effective in animal tests, and therefore are useful in the treatment of central nervous system diseases: for example, sexual dysfunction such as impotence, obesity, appetite regulatory disorders such as hyperphagia or anorexia,

anxiety, depression, sleep disorder and the like.

[0072]

A medicinal composition having as effective component not less than 1 to 2 species of the compounds (I and II) of the present invention or pharmaceutically acceptable salts thereof can contain a pharmaceutically acceptable carrier; this is prepared as tablet, powder, subtle granule, granule, capsule, pill, solution, injectable, suppository, ointment, skin patch or the like, using a carrier, a diluting agent or other additives that are commonly used in drug preparation; and this is administered orally (including sublingual administration) or non-orally.

Clinical dosages of the compounds (I and II) of the present invention or pharmaceutically acceptable salts thereof in humans are suitably determined on a case-by-case basis, with consideration for the symptoms, body weight, age and sex of the patient in which is to be used, the administration route and the like; in general, it is administered orally in a range of 1 mg to 1000 mg per day per adult, and preferably 50 mg to 200 mg, once daily or divided into several doses per day, or it is administered intravenously in a range of 1 mg to 500 mg per day per adult, once daily or divided into several doses per day, or it is continuously administered intravenously within a range of 1 hour to 24 hours per day. As a matter or course, as mentioned above, since the dose varies depending on a variety of conditions, there are cases where smaller amounts than the above-mentioned doses are sufficient.

[0073]

Tablets, powders, granules and the like are used as solid compositions for oral administration of the present invention. In such a solid composition, one or more active substance is mixed with at least one inactive diluent, for instance, lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone or magnesium metasilicate aluminate. The composition may, according to methods of the art, contain additives other than inactive diluents, for example, lubricants such as magnesium stearate, disintegrants such as calcium cellulose glycolate, stabilizers such as lactose, and solubilizers such as glutamic acid or aspartic acid. The tablet or pill may, if necessary, be coated with a sugar coating such as sucrose, gelatin, hydroxypropylcellulose and hydroxypropyl methylcellulose phthalate or with a gastrosoluble or enterosoluble film.

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs and the like, and contain commonly

used inactive diluents, such as, purified water or ethanol. In addition to the inactive diluent, this composition may contain an adjuvant such as a solubilization or dissolution promoting agent, a wetting agent or a suspending agent, a sweetener, a flavorant, an aromatic agent or a preservative.

[0074]

Injectables for non-oral administration include sterile-water based or non-water based solutions, suspensions and emulsions. Water based solutions and suspensions can contain, for instance, distilled water and physiological saline for injectables. For example, propylene glycol, polyethylene glycol, plant oils such as olive oil, alcohols such as ethanol, Polysorbate 80 (product name) and the like are available for non-water soluble solutions and suspensions. Such a composition may further contain additives such as an isotonization agent, a preservative, a wetting agent, an emulsifier, a dispersant, a stabilizer (for instance, lactose), and a solubilization or dissolution promoting agent. These are sterilized by, for example, filtration through a bacteria-retaining filter, admixture of a bactericide or irradiation. These can also be prepared as sterile solid compositions and dissolved in sterile water or a sterile injection solvent prior to use.

[Document Title] Abstract

[Abstract]

[Problems to be Solved]

An object of the present invention is to provide a 5-HT_{2c} agonist having a benzazepine derivative, or a pharmaceutically acceptable salt thereof, as effective component and to provide novel benzazepine derivatives or pharmaceutically acceptable salts thereof.

[Means for Solving the Problems]

5-HT_{2c} agonist having a zenzazepine [*sic*] derivative or pharmaceutically acceptable salt thereof as effective component and novel zenzazepine [*sic*] derivatives that are 5-HT_{2c} agonists, or pharmaceutically acceptable salts thereof.

[Selected Drawing] None